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BRITISH MEDICAL BULLETIN

Congenital Factors in Disease

GENETICS AND CLINICAL MEDICINE
VITAL STATISTICS OF STILL-BIRTHS AND NEONATAL DEATHS
PATHOLOGY OF STILL-BIRTH AND NEONATAL DEATH
POST-MORTEM EXAMINATION OF THE NEWBORN
BLOOD-GROUPS AND CONGENITAL DISEASE
RUBELLA AND CONGENITAL DEFECTS
PRENATAL NUTRITION AND INFANT DEVELOPMENT
CONGENITAL VISUAL DEFECTS
GENETICS OF CANCER
MENTAL DEFECT

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CORRIGENDUM

GUIDE TO THE JOURNALS

Congenital Factors in Disease

CONGENITAL FACTORS IN DISEASE has been chosen as a descriptive title for this number, although it is realized that there are certain objections to the use of the term " congenital ". As Professor Crew points out, " congenital " has no etiological significance, but refers simply to a point in time. Nevertheless, the term has its convenience as an indication of defects determined before birth, whether genetically, environmentally (as an effect of maternal disease during pregnancy), or as a genetically-determined environmental incompatibility (as in erythroblastosis foetalis).

PROFESSOR F. A. E. CREW was for many years director of the Institute of Animal Genetics, University of Edinburgh. During the recent war he was appointed as director of medical research, and later as director of biological research, to the War Office. More recently, he was appointed to the Bruce and John Usher chair of public health in the University of Edinburgh. With his translation to the chair he now holds, its title has become changed to indicate its enlarged scope and is now the chair of public health and social medicine. He is the author of *Animal genetics* (1925) ; *Organic inheritance in man* (1927) ; *Sex determination* (1933), and of numerous other publications dealing with these and related matters. In the dual capacity of physician and geneticist, Professor Crew speaks with unusual authority on those wider aspects of medicine in which inheritance plays an important part, and his article in this number provides a characteristically stimulating introduction to the subject.

DR. B. WOOLF, who contributes the second article in this number, is lecturer in medical statistics in the University of Edinburgh, where he is building a statistical research unit willing to assist and co-operate with all medical and social agencies in Scotland in research projects in the field of social medicine. He has made a detailed statistical study of the relation between social conditions and infant mortality, of which part 1 has been published (*J. Hyg., Camb.* 1945, **44,** 67) and part 2 is to appear in the new *British Journal of Social Medicine*, which is to be published by the British Medical Association under the joint editorship of Professors F. A. E. Crew, Lancelot Hogben (who has such diverse achievements to his credit as the authorship of *Mathematics for the million* and of the *Xenopus laevis* test for pregnancy), and J. A. Ryle. Dr. Woolf began his research career as a biochemist under Sir Frederick Gowland Hopkins at Cambridge, and has published papers on bacterial metabolism, enzyme action, the chemistry of immunity, and other topics. Becoming increasingly interested in the social aspect of medical problems, he acquired a knowledge of modern statistical theory and practical computational methods, and accepted an invitation from Professor Lancelot Hogben to come to Birmingham University to lecture and research on social biology. During the war he was engaged for a time on medical statistical research at the War Office.

DR. AGNES R. MACGREGOR is lecturer on pathology of diseases of children in the University of Edinburgh, pathologist and bacteriologist to the Royal Hospital for Sick Children, Edinburgh, and pathologist for infants to the Edinburgh Royal Infirmary. She was formerly a lecturer on pathology and bacteriology in the School of Medicine of the Royal Colleges, Edinburgh. For some years, Dr. Macgregor has made a special study of neonatal pathology and her published work includes papers on this subject, as well as on pneumonia and tuberculosis in childhood. For two years during the war she was a member of a team engaged in an inquiry on behalf of the Medical Research Council into the incidence of tuberculosis due to human and bovine type tubercle bacilli throughout Scotland.

DR. H. S. BAAR holds the degrees of M.D. and Ph.D. of Vienna, and was for 20 years on the staff of the St. Anna Children's Hospital in that city. In December 1938 he was appointed research Fellow at the Children's Hospital, Birmingham, where he subsequently became research pathologist. Dr. Baar has published a book on haemotology in childhood, a monograph on alimentary anaemias, and over fifty scientific papers. At present he is engaged in work on the pathology of an infective encephalitis of the newborn transmissible to animals, and in the preparation of a paper on the pathology of fibrocystic disease of the pancreas—upon which a preliminary communication was read before the Association of Clinical Pathologists in January 1944.

DR. R. R. RACE is well known as the leading British worker on the genetics of human blood-groups. He has previously contributed to this Bulletin a review of knowledge of human blood-groups (with G. L. Taylor ; *BMB* **420**) and a note on their inheritance (*BMB* **421**).

SIR LEONARD G. PARSONS is dean of the faculty of medicine and professor of children's diseases at Birmingham University. He is one of Britain's most distinguished paediatricians, and was President of the British Paediatric Association in 1942-44. He has made important contributions to the literature of paediatrics. News of the knighthood just conferred upon him reached us as we were going to press.

DR. A. ST. G. HUGGETT is physiologist to St. Mary's Hospital Medical School, and professor of physiology in the University of London. He was a pupil of the late Professor John Mellanby, F.R.S., and of Dr. John Fairbairn at St. Thomas's Hospital. He inherited from Professor Mellanby an interest in the coagulation of the blood which led to work on the dyestuff anticoagulants, including chlorazol pink. He has been responsible for initiating the experimental approach to foetal physiology of the last twenty years, on which subject he has published many papers.

PROFESSOR A. SORSBY is the first holder of the research chair in ophthalmology which was in 1943 jointly established by the Royal College of Surgeons and the Royal Eye Hospital, London. A note on Professor Sorsby appeared in volume 1 of this Bulletin, to which he contributed an article on " The task of ophthalmological research " (*BMB* **160**).

DR. G. M. BONSER is Brotherton Fellow in cancer research in the University of Leeds, and pathologist to the Seacroft Laboratory of the Emergency Medical Service. She has been engaged in cancer research for twenty years, working first on intrathoracic cancer and later on the hormonal and genetic aspects of mammary and testicular cancer. She has established a strain of mice particularly susceptible to carcinogens applied to the skin. Her publications include papers on " The incidence of intrathoracic cancer in Great Britain with special reference to Leeds " (*Acta, Union internat. contre Cancer*, 1938, **3,** 119); " The hereditary factor in induced skin tumours in mice : establishment of a strain specially sensitive to carcinogenic agents applied to the skin " (*J. Path. Bact.* 1938, **46,** 581) ; " A microscopical study of the evolution of mouse mammary cancer : the effect of the milk factor and a comparison with the human disease " (*J. Path. Bact.* 1945, **57,** 413).

PROFESSOR L. S. PENROSE studied psychology at Cambridge and also graduated there in medicine. His work has been concerned with the influence of heredity on diseases and especially with the genetics of mental conditions. He has written many papers on mongolism, phenylketonuria, statistical analysis of the effects of shock therapy in psychosis, etc., and a standard book, *Mental defect*. He has also assisted in devising intelligence tests, which have been widely used in the British and Canadian armies. For some years his researches into the causation of mental defect were carried out in co-operation with the Medical Research Council at the Royal Eastern Counties Institution, Colchester. Before his appointment to the Galton Chair of Eugenics at University College, London, he was Director of Psychiatric Research for the Province of Ontario, Canada.

THE PLACE OF GENETICS IN CLINICAL MEDICINE

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Introductory

It is undoubtedly the case that an understanding of genetic principles on the part of the clinician has been made more difficult by recent elaborations in genetic theory. In the text books of 35 years ago heredity was, along with syphilis, alcoholism and chronic lead poisoning, all too often the refuge of the diagnostically destitute. In the era of the unit character of Mendelism, gene—the cause, and character—the effect, were very simply and precisely related. But since then and as the result of the exceedingly rapid advances in genetic theory and methodology these earlier simplicities have given place to such complexities that genetics has failed to become that which it promised to be—an easily used instrument of precision in the hands of the diagnostician.

The term "genetic" still means that the cause of the condition being considered was present within the fertilized ovum in which the individual had its origin, having been transported thereinto by the chromosomes of the nucleus of the spermatozoon, of the ovum, or of both. But it has come to mean much more than this. The cause is now a particular gene resident at a particular point along the length of a particular chromosome. Though the nature of genetic action is even yet not known, it is reasonably assumed from its effects and by analogy that it takes the form of a "chemical" impress upon the processes of development or of degeneration. This influences in a particular way the rate or direction of one or more of these processes as they shape a particular tissue(s), organ(s) or organ system(s). Thus it is that the genotype, the sum total of all the genes in the hereditary constitution of an individual, representing and delimiting all the hereditary possibilities of the individual, is the architect of its characterization, its phenotype, the sum total of its characters, its details of structure and function.

Nature : Nurture as Cause

But the geneticist no longer presents the view that the gene alone is always the cause of the character. There are certain characters, for example, those of the blood-groups and of the eye-colours, which would seem to be the direct expression of particular genes unaffected in their action by any extrinsic agency. But in the fashioning of the great majority of characters, normal and abnormal, both nature and nurture, both genotype and environment, have had a hand. The gene in action is an impulse inclining development in a certain way. But the developing structures are exposed to and react to the impress of other agencies, e.g. local stimuli derived from neighbouring structures, blood-borne stimuli. They can be affected by agencies in the external world of the individual of which they are part. Save for peculiarities such as accidental mutilation it seems probable that genotype and environmental agencies are always concerned, though not always equally, in the fashioning of any given character, and that even in instances of deficiency and infectious diseases there is a genetic difference between those who exhibit a proneness to react in such a way as to exhibit the condition and those who do not.

It is this duality in causation, the genetic inclination and the environmental provocation, that tends to make clinical genetics decidedly difficult. To disentangle the two in the case of the species which lives in an environment created by itself, and which is notable for its variety, must present considerable difficulties when the species itself reproduces so slowly, has so few offspring, fails to maintain pedigrees, and cannot be used as experimental material. It has been necessary to devise highly sophisticated mathematical techniques for the purpose. Nevertheless, it is this very fact that usually there are two causal factors very different one from the other, one being deeply hidden and protected within the constitution of the individual, the other being present in the individual's environment and therefore more or less exposed to measures of control, that has permitted medicine so frequently to disregard the genetic factor and to concentrate upon the control and prevention of the action of the environmental causes. Though the gene cannot be excised from a population save by measures of non-propagation it is often possible to prevent the provocative action of the environmental agent and thereby to nullify the action of the gene.

If, for example, in the aetiology of a condition such as tuberculosis there is a combination of a genetic proneness and an environmental provocation, the latter being a configuration of the bacillus together with a variety of unsatisfactory social conditions, then by controlling and removing the latter the former must lose all its significance. Smallpox in its most virulent form doubtless overrides all genetic differences in respect of resistance, but with lessened virulence the more resistant individuals within a population would be far less likely to succumb. During the course of several millennia it might quite well come to pass that, through the selective elimination of the relatively susceptible, a human stock would ultimately consist solely of the relatively resistant.

But it is not the way of medicine to wait upon natural selection. Through vaccination, medicine, disregarding all genetic considerations, has artificially raised (or could have raised) the resistance of all, and this in less than a hundred years. Manifestly medicine is right in thus neglecting the genetic cause in conditions of this kind. There is undoubtedly a genetic cause of Mongolism, but the gene(s) that lies at the root of this character requires a special intra-uterine environment in which to gain expression. The repair of this environment in attempts to eradicate Mongolism would seem to be a far easier task than attempts to eliminate the gene. It will probably be found that the production of many of the so-called congenital diseases as listed by the Registrar-General, congenital meaning that the abnormal characters are displayed by the newly-born, is similarly the result of the interaction of particular genotypes and peculiar agencies within the maternal environment. If this is so, then the prevention must take one of two forms ; that of removing by continued selection the causal gene from the population, or that which removes or overwhelms the causal factors within the environment.

The use of the term "congenital" in connection with causation is both mistaken and misleading. It is a point in time and not a cause. It is one of a series of terms, intrauterine (place and time), foetal (state and time), stillbirth (condition and time), congenital (really natal?), neonatal, infant (state and time), all indicating the time during the early life history of an individual when the character—genetic, acquired, and genetico-environmental in causation—is displayed. Congenital used in this sense is more inexact than many of the others since a character that is present when the child is born was, in the majority of instances, displayed by the foetus.

But we now know that not only is the gene in its action influenced, sometimes quite profoundly, by environmental agencies, we know also that the action of any one gene within the genotype can be affected equally profoundly by the action of companion genes. The genotype of a given individual includes thousands of different genes, and the genotypes of no two individuals, excepting identical twins, are alike. Each gene exerts its action amid a vast company of genes, and its stimuli are pooled with those of all the rest. Very few genes, if any, influence the development of only one character. No wonder, then, that its action may be prevented, neutralized, overwhelmed, reinforced, modified by that of certain others. In fact, it is firmly established that one and the same gene can yield quite different end-results in different genetical milieux, just as it can in different external environmental conditions. But although these facts tend to make an understanding of genetic theory more difficult, they do not prevent us from detecting gene action when it is present or from regarding a particular gene as being the prime cause of a given character.

Genetics has lost some of its attractions to the clinician during the last decade because many who yearn ardently for social betterment have derived from it certain notions that are indeed extravagant. Those who so eagerly claim that we should do for ourselves that which we have done through the application of genetical knowledge with our domesticated animals and cultivated plants, would seem to forget that those who, by manipulating the processes of organic inheritance, sexuality and reproduction, have produced the magnificent breeds and varieties, were able to construct for themselves a standard of an ideal and thus congregate in one and the same stock that constellation of characters which most closely approached this. Through the applications of genetics it is possible to do much in the fashioning of future generations, but for the existing generation genetical knowledge can do very little.

In the case of mankind we have no firm standard of the ideal constellation of human characters. In the second place it simply is not true that the major problems of civilization refer to limitations in the ability of man to control his own nature and his external world. They arise directly from imperfect co-ordination of human effort. It can perhaps be agreed that we should imitate the example of the great livestock breeders, but if we do we must give, as they gave, as much attention to the environment as to the genotype. We, like them, can begin to consider the application of genetic principles when we have created an optimum environment. It is only when such an environment has been provided that we shall know which undesirable characters, as well as desirable, are caused wholly or partly by environmental agencies, and in the production of which the genotype is largely or mainly concerned. For the present and for a long time ahead, it is undoubtedly the case that the most rapid improvement will be secured through the control of the environmental agencies which promote health and evoke disease.

In spite of all the difficulties and of all the extravagances it is utterly reasonable to foster the growth of clinical genetics as a branch of medicine which is concerned with future generations no less than with the present. Scientific therapy, prognosis and diagnosis all must wait upon aetiology. Exactness in aetiology means precision in all the rest. One cause, and by no means an unimportant one, of abnormality is undoubtedly the gene. The recognition that gene action is involved in the production of a particular pathological character is usually based upon the distribution of that character amongst individuals related to the propositus. The family pedigree is still the main source of our knowledge of human genetics. The fact that a certain pathological condition is displayed by members of the same family is not proof, of course, that the condition is genetic in its causation, since the family is a vehicle for social as well as organic inheritance, and a purely environmental causal agent operating upon different individuals in different generations can evoke the same reaction. It is not merely the distribution of a character within a pedigree but the significant peculiarities of this distribution that indicates the action of a gene.

The Characteristic Features of Complete Dominance

1. The affected individual has an affected parent.
2. The offspring of affected × normal include affecteds and normals in approximately equal numbers. This is so because the great majority of affecteds are heterozygous.
3. All normals related to affected individuals are in every way normal and produce, when mated with normals, none but normals.
4. A single pedigree covering three generations and including both normals and affecteds is as often as not quite sufficient to reveal the genetic nature of the abnormality.

In the case of a gene that is completely dominant, to observe the transmission of the character is to witness the distribution of the gene. Examples: brachydactyly, synphalangy, alkaptonuria, congenital stationary night-blindness, congenital cataract, multiple telangiectasia (Osler's disease), epiloia, keratosis follicularis (Darier's disease), Huntington's chorea. These examples are offered in order to illustrate certain points.

In the case of complete dominance it would be, if it were thought desirable, easily possible to eliminate the gene from the future population as, by the withholding of propagation from those who exhibit the character, the transmission of the gene, the presence of which is revealed by the character, would be prevented. There would seem no reason whatsoever for suggesting such action in the case of conditions such as synphalangy, since what the gene has done the surgeon's knife can repair. In the case of Huntington's chorea there is a peculiar difficulty since the average age of onset of this condition is around 35, so that an affected individual can have reproduced long before the disease displays itself. Epiloia is an example of a disease that commonly kills in infancy, only mild cases surviving to reproduce their kind. It follows therefore that mild can

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beget severe, and the differences between affected parent and affected offspring must be referable to the action of modifying genes or circumstances. Since the chances that the progeny of (heterozygous) affected and normal will be affected or normal are equal, it may be thought reasonable to advise parents who have produced an abnormal child to have no others. Completely dominant genes yielding characters that are gravely disadvantageous or incompatible with continued life tend to eliminate themselves, since they destroy the individual either *in utero*, in infancy or adolescence, before that individual can reproduce. If, then, they are not infrequent in a population their prevalence must be due in part to the occurrence of fresh mutation. If in an affected individual the character is due to a mutation during the life-history of that individual, it follows that the parents of that individual would be normal.

The Characteristic Features of Complete Recessivity

1. The gene may be handed down through many generations unsuspected and unexpressed and only when two individuals, each heterozygous in respect of it, mate and reproduce, is the homozygous exhibitor of the character to be expected.

2. The vast majority of affected individuals are the offspring of parents who phenotypically are normal, but who are in fact heterozygous. Thus organic inheritance would not seem to be concerned in the aetiology of the condition.

3. Amongst the offspring of two such heterozygotes the expected ratio of normal to affected is three to one.

4. There is a familial incidence, more than one individual in a sibship being affected. The exhibition of the character is significantly more than common amongst the offspring of consanguineous marriages.

5. The offspring of affected × normal are invariably normal, those of affected × affected invariably affected.

6. For the recognition of gene action in such cases a single pedigree is of no value. Few pedigrees proffer full details of three generations. It is the pedigree that is pockmarked with abnormality that is recorded ; one in which the abnormality is rare is seldom available, and thus it is that false impressions are so often gained. The use of a single pedigree is that it can be pooled with others of the same kind. It is to the literature on the subject that the diagnostician must turn.

Examples : infantile amaurotic idiocy, alkaptonuria, albinism.

It is to be noted that the possessor of a recessive gene in the heterozygous state does not exhibit the character and cannot be distinguished from the individual in whom this particular gene is not present. It is for this reason that any attempt to eradicate the gene from a population by controlled reproduction becomes an almost impossible task. Any control of the exhibitors of the character would leave the far greater number of the heterozygous untouched. The reason why there is a greater concentration of a recessive character amongst the offspring of consanguineous marriages is that first cousins, for example, are individuals who have received in common chromosome material and therefore genes from the same pair of grandparents and that this chromosome material is therefore more likely to include the same recessive genes. If two parents produce an amaurotic idiot, for example, the odds are that one half of their offspring will possess the gene and one quarter will exhibit the character. The latter eliminate themselves, the former will survive to carry the seed of death which they will pass on in their turn. It is reasonable, therefore, seriously to consider the desirability of advising such parents to reproduce no more.

The inclusion of alkaptonuria in this list as well as in the last introduces an interesting though somewhat puzzling phenomenon. It is clear from pedigree studies that a character such as alkaptonuria can be based on a dominant gene in certain instances, on a recessive gene in others. This observation would seem on first sight to remove all precision from genetical teaching, but this is not so. A character is the end-result of a long and intricate developmental process(es) which may be affected at quite a number of critical points during its course by the incoming of a fresh stimulus. To the character itself there must be a fairly narrow limit in the variety of its final form. There is no reason why more than one gene, although acting in different ways and at different times during development, should not lead to the same end-result. That this is so does not in the least destroy genetic theory or the clinical value of genetical knowledge.

But there is something even more difficult of acceptance than this. Dominance and recessivity are not final static properties of genes. We know that each of them can be either complete or incomplete ; in fact, not uncommonly an individual who, according to the rules, should exhibit a dominant character lacks it although undoubtedly the gene is within him. The fact is, as has already been stated, that a gene in its action is exposed to and reacts to the action of many another gene in the genotype. In different gene companies this action becomes greatly altered and modified. Its penetrance, the degree or percentage of its expression as a character, can vary very greatly, being affected by the action of other genes and by that of environmental agencies.

Mutation implies a disturbance of a genotypic equilibrium. If a mutant gene behaves as a complete dominant from its very beginning this disturbance is immediate ; if it is recessive its action is overwhelmed by its unmutated partner gene, and so there is no such disturbance. But if in the genotype in which a dominant mutation finds itself there happen to be genes which modify this action, its effects would be incomplete or even resemble that of a recessive. In general, it can be said that advantageous mutant genes tend to become dominant in their action, while deleterious genes tend to become recessive. This does not indicate any change in the gene itself. It merely means that in many instances a block of genes is concerned in the production of a character, the key gene being the prime agent and the rest being modifiers.

The Characteristic Features of Dominant Sex-linked (X-borne) Inheritance

1. All affected individuals have an affected parent.

2. The character is transmitted only by affected individuals and by them to approximately half their offspring.

3. Affected males × normal females have only affected daughters and normal sons.

4. The character is twice as common amongst females as amongst males for the reason that there are twice as many X-chromosomes in the female population.

5. A single pedigree can suffice to reveal the genetic nature of the character.

6. All unaffected individuals lack the gene.

Example : defective enamel of the teeth.

It will be noted that in the main the characteristic features of this type of inheritance are similar to those of ordinary

completely dominant autosomal inheritance. The two are to be distinguished by the peculiar sex-distribution as detailed in 3 and 4 above.

The Characteristic Features of Recessive Sex-linked (X-borne) Inheritance

1. The majority of affected individuals are males and have phenotypically normal parents.
2. An affected female must have had an affected father and a heterozygous or affected mother.
3. The recessive gene can be handed down unsuspected and unexpressed through one or even two generations, but it is most unlikely, unless families are exceedingly small, that it will pass through three generations without the appearance of an affected male.
4. A single pedigree, if sufficiently large, can suffice to reveal the genetic nature of the character.

Examples : haemophilia, red-green colourblindness.

Perhaps the most characteristic feature of the sex-linked mode of hereditary transmission is criss-cross inheritance. In the case of a dominant X-borne gene, the mating of an affected father with a normal mother yields affected daughters (taking after their father) and normal sons (taking after their mother). In the case of a recessive X-borne gene, the mating of a normal father with an affected mother produces affected sons and phenotypically normal daughters.

Partial Sex-linkage

In man the Y-chromosome consists of a pairing segment which carries alleles of the genes on the corresponding portion of the X-chromosome, and a non-pairing segment which contains a few genes without such alleles. The mode of transmission of the genes on these homologous and non-homologous portions of the Y respectively is therefore significantly different.

The characteristic feature of the mode of transmission of a character whose gene is resident upon the non-homologous, non-pairing segment of the Y-chromosome, is that only males exhibit the character and each affected male transmits the character to all his sons. The gene material in this non-pairing segment is the peculiar possession of the male. The character follows the track of this segment from generation to generation.

Example : webbed toes.

It does not follow, of course, because a given character is restricted in its exhibition to males, either that it is genetic in origin or that its gene is Y-borne. Manifestly, pathological conditions of the seminal vesicles are of necessity restricted to the male. Pattern baldness, an autosomal gene, yields a character that is likewise restricted to the male, but for the reason that it is a gene that can find expression only in a male somatic milieu.

But crossing over between the homologous portions of the X and Y means that Y-borne gene material can be incorporated in the X and *vice versa*. These segments behave as do autosomes in this respect, and therefore the mode of inheritance of dominant and recessive characters with genes resident in these pairing segments of the X and Y will be similar to that of autosomal characters, but with this difference : variations in the frequency of crossing-over will result in a sex-ratio among the affected offspring that is significantly different from that of equality which obtains in the case of autosomal characters. Though this is a matter that is intellectually attractive it is one that has no practical value in clinical genetics.

Examples : total colourblindness, xeroderma pigmentosum, Oguchi's disease, recessive epidermolysis bullosa, dominant and recessive forms of retinitis pigmentosa.

Such evidence as presently exists seems to indicate that the dominant and the recessive genes which yield retinitis pigmentosa are, in fact, alleles—that is to say, each occupies the same locus in the X, each being a mutant form of the " normal " gene.

Multiple Allelomorphic Series

Mutation implies an alteration in the internal organization of a gene resulting in a changed action of that gene and yielding a different end-result. The gene undergoes change, but the developmental processes it affects remain the same. The mutant gene occupies the same locus in the chromosome as did the unmutated gene from which it arose and which it replaces. In this locus there can be one or the other but not both. The original gene or its mutant form can mutate again and again to yield a series of multiple allelomorphs, of which only one can occupy the particular locus. Since there are two chromosomes in every pair (the non-homologous section of the Y being disregarded), it follows that an individual can possess any two members of a multiple allelomorphic series.

Such a series, of the greatest interest to the clinician, is the A_1, A_2, A_3, B and O of the blood-group characters, A_1 being dominant to A_2, A_3 and O, A_2 to A_3 and O, A_3 to O, and B to O. When any of the A's and the B are present in the same individual, both are expressed.

Conclusion

This brief and most imperfect review may have sufficed to display the gifts that genetics offers to clinical medicine and to disclose the difficulties that surround them. It is manifest that rarely can the clinician expect to receive simple, straightforward, unequivocal answers to the questions he asks. Well may he doubt the usefulness to himself of a science whose every utterance seems to demand elaborate qualification. It cannot be that the complexities of the science repel him. He readily turns for help to biochemistry, a science no less specialized or complicated. But biochemistry places tools in his hands that he can profitably use in diagnosis and therapy. It does not deal so much with causes as with the nature and production of causes. Diabetes mellitus is in certain instances the expression of a dominant autosomal gene whose action is to yield abnormality in the functioning of the pancreas. Neither geneticist nor clinician can reach the gene, but the biochemist can demonstrate the nature of the effects of the action, discover insulin, and place an instrument of great potency in the hands of the clinician. Insulin therapy owes nothing to the gene. The geneticist can help to prevent the occurrence of diabetes mellitus in the next generation, the biochemist can provide the means of control of this condition in the existing generation. The treatment of haemophilia is not influenced by the fact that its causal gene is an X-borne recessive, though the explanation of its aetiology and incidence is solely genetical.

The main role of genetics in clinical medicine has been that it has furnished scientific factual knowledge on which advice concerning habits, behaviour and reproduction can

be built. Since the patients of the clinician are the children yet unconceived no less than the individuals of the existing generation, genetics can rightly claim a place in his equipment.

It has been the expansion of blood transfusion as a service that has given to genetics a firm and prominent place in clinical medicine. The knowledge which is purely genetical and which relates to the blood-group characters is now an essential part of the equipment of the modern clinician. The A B O multiple allelomorphic series, the M and N genes, the Rhesus genes, are as familiar to the clinician, the obstetrician, the pediatrician, as are any of the causal agents of bacteriology. In order to deal with their effects it is necessary to know them, and to know them is to know genetics and to appreciate the value of this science in its applications to clinical medicine.

If medicine and the rest of the sciences that are being used by society for its own betterment flourish there will come a time when the environmental agencies that evoke disease are conquered. Then will be disclosed the hard core of the genetical varieties of physical frailty and mental defect and deficiency, for the treatment of which genetical measures derived from genetical knowledge may be required. For this reason it is desirable that even now every effort should be made to expand our knowledge of human genetics in order that, when wanted, the appropriate instruments of therapy may be found sharpened and ready in our armamentarium.

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VITAL STATISTICS OF STILL-BIRTHS AND NEONATAL DEATHS

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A still-birth is a baby of 28 weeks or more maturity since conception, who is delivered without showing any signs of life. Just before the war, there were about 25,000 still-births registered in England and Wales every year. About 607,000 babies were born alive, and of these, about 18,000 were dead within four weeks and 35,000 within a year. The total wastage of life during birth and infancy was thus about 60,000 a year. The natural increase (excess of live births over deaths at all ages) was about 119,000 a year. An annual loss of 60,000 potential citizens, in a period of public concern about the imminent decline in the country's population, is obviously a matter calling for serious investigation. I propose in this paper to state and discuss some of the facts about the vital statistics of still-births and deaths in early infancy, with special attention to the light they throw on the question of how far these deaths can be regarded as avoidable at the present stage of medical and social knowledge.

About half the infant deaths before the war were certified as due to infectious processes, the big cause-groups being bronchitis and pneumonia, diarrhoea and enteritis, and the common infectious diseases, mainly whooping cough and measles. The great majority of these deaths occurred in infants more than a month old. The other half of the infant deaths was ascribed to the group of causes sometimes called "developmental and wasting diseases", and sometimes "congenital causes", and mainly affected infants during the first four weeks of life. There are thus good grounds for making a distinction between neonatal deaths (at ages less than four weeks) and postnatal deaths (these during the remainder of the year of infancy). Still-births and neonatal deaths form a natural aetiological grouping, in which the main influences are foetal defects, unfavourable intra-uterine conditions, the hazards of the birth process, and adverse environmental circumstances acting on the child indirectly through the mother.

During the five years 1934 to 1938 inclusive, the average infant mortality in England and Wales was 56·9 deaths per 1,000 live births, of which the neonatal rate was 30·0. Deaths in the "congenital causes" group gave a rate of 30·9. The rates attributed to the various diagnostic categories included under this heading are shown in Table I. More than half the deaths are associated with prematurity, and one-fifth with congenital malformations.

TABLE I. DEATHS FROM "CONGENITAL CAUSES": MORTALITY-RATES PER 1,000 LIVE BIRTHS, ENGLAND AND WALES, 1934-38

Congenital malformations	6·02
Congenital debility	2·30
Premature birth	16·83
Atelectasis	1·95
Icterus neonatorum	0·53
Disease of the umbilicus	0·13
Pemphigus neonatorum	0·11
Other diseases of early infancy	0·53
Injury at birth	2·46
Total	30·86

These national averages conceal quite wide differences between different strata of the population. An indication of the variation in the rates with social and economic status is provided by Table II. In his 1931 *Decennial supplement*,

TABLE II. MORTALITY FROM CONGENITAL CAUSES FOR LEGITIMATE INFANTS BY SOCIAL CLASS OF FATHER, ENGLAND AND WALES, 1930-32

Social class	I	II	III	IV	V	All
Congenital malformations	5·0	5·4	5·6	5·7	5·4	5·5
Congenital debility	1·4	2·2	2·9	3·3	3·8	3·0
Premature birth	10·5	14·4	16·8	18·6	19·6	17·3
Injury at birth	2·3	2·5	2·1	2·0	2·0	2·1
Other causes	2·8	3·0	2·7	2·9	3·0	3·0
Total	22·0	27·5	30·1	32·5	33·8	30·9

part IIa (occupational mortality), the Registrar-General divided the occupied males into five social classes. Class I comprised the higher business and professional occupations, Class III the skilled workers, and Class V the unskilled. The other classes were intermediate, Class II being mainly the lower professional and business grades, and Class IV semi-skilled workers. The average infant mortality during 1930-32 is given for each class, analyzed by cause and by age at death. The table shows the rates for the congenital causes group, and for the various sub-headings in so far as they are separately distinguished. It will be seen that the total mortality of 33·8 in Class V is more than 50% higher than the rate in Class I. Congenital malformations and other causes show no consistent class gradient, and injury at birth decreases slightly as one descends the social scale. But congenital debility and premature birth go up quite steeply with increase in poverty. Class V shows nearly double the mortality of Class I from premature birth, and over 2½ times the rate for congenital debility. The whole of the difference between Class I and Class V is accounted for by the excess under these two headings.

Still-birth rates are usually calculated by the formula

$$\frac{\text{Number of still-births during year}}{\text{Number of live births + still-births during year}} \times 1{,}000$$

The rates are thus not quite comparable with those for infant mortality, which are given per 1,000 live births. In England and Wales during 1934-38, the still-birth rate, calculated as above, was 39·7. The still-birth rate, per 1,000 live births, was 41·3, as compared with the neonatal mortality-rate of 30·0. In England and Wales there are no figures available for still-births analyzed by cause or by social class.

Registration of still-births in Scotland did not begin until 1939, and an analysis for this year by social class of father was made by the Registrar-General for Scotland. The results are shown in Table III. It will be seen that in the

TABLE III. STILL-BIRTHS ACCORDING TO SOCIAL CLASS OF FATHER, SCOTLAND, 1939. RATES PER 1,000 TOTAL BIRTHS, LIVE AND STILL

	Social class					
	I	II	III	IV	V	All
Large burghs	30·0	35·5	41·8	43·1	44·0	42·1
Counties (excluding large burghs)	38·7	39·6	48·7	33·6	39·0	42·5
Scotland	33·9	37·8	44·5	38·0	42·4	42·2

large burghs (the 24 largest towns) the rate rises steadily with fall in economic status, Class V having a rate about 50% higher than that for Class I. In the county areas there is no clear trend, and Class III gives much the highest rate. This anomalous result may be at least partially explained by the mode of allocation of occupational groups to the different social classes. In particular, mortality-rates among infants of coal miners are excessively high. This is discussed below. The majority of coal miners are assigned to Class III, and there are probably enough miners in the Scottish counties to give an anomalously high figure for Class III. Nevertheless, the irregularity of the figures for Scottish counties does suggest that economic status is not the only important social agency influencing the incidence of still-births.

In Scotland, but not in England and Wales, the law requires registration of the cause of each still-birth. The data are tabulated in considerable detail by the Registrar-General for Scotland, and the figures for 1939 to 1943 are summarized in Table IV. In view of the difficulty of fixing the cause of a

TABLE IV. CAUSES OF STILL-BIRTHS, SCOTLAND, 1939-43. RATES PER 1,000 TOTAL BIRTHS, LIVE AND STILL

	1939	1940	1941	1942	1943	Mean
General diseases in mother	0·9	0·9	1·3	1·2	1·2	1·1
Toxaemias in mother	3·8	4·4	4·0	4·2	3·4	4·0
Ante-partum haemorrhage	5·4	5·0	5·1	5·2	4·3	5·0
Difficult labour	9·5	8·9	11·3	10·4	9·3	9·9
Foetal malformations	5·9	6·1	6·5	6·8	6·1	6·3
Other defined causes	2·9	3·1	3·2	4·2	4·5	13·3
Undefined causes	13·9	13·7	8·1	6·3	6·9	
All causes	42·2	42·1	39·6	38·2	35·6	39·6

still-birth with any certainty, the table shows remarkably high consistency in the main cause groups from year to year. The only large change has been a fall in the undefined causes and a corresponding rise in the miscellaneous defined causes. It may be taken that certification, if not accurate, is at any rate biased in the same way in different years. The mean rates for the five years can be summarized as follows :

Conditions affecting the mother (general diseases, toxaemias and haemorrhage)	10·1
Difficult labour	9·9
Foetal malformations	6·3
Other causes, defined and undefined	13·3
Total	39·6

To obtain the total mortality from congenital malformations, one must combine the still-birth rate and that for live-born infants. In Scotland, during 1939-43, the average infant mortality from congenital malformations, calculated per 1,000 total births, was 6·3—exactly the same as the rate among still-births. The total mortality was thus 12·6 per 1,000 total births, or 13·0 when reckoned per 1,000 live births.

Still-birth and neonatal mortality-rates are influenced by three groups of etiological agencies :

1. Biological.
2. Social and economic.
3. Medical and nursing facilities.

The biological differentials include parity of birth, age of mother, and sex of infant.

Birth-Parity and Maternal Age

Figures showing the variation in still-birth rates with parity and age of mother are shown in Table V. The data are

TABLE V. SINGLE STILL-BIRTHS PER 1,000 SINGLE LIVE-BIRTHS BY PARITY AND AGE OF MOTHER, ENGLAND AND WALES, 1939-40

Age of mother	Order of birth											
	1	2	3	4	5	6	7	8	9	10	11-14	All
15–19	27	18	—	—	—	—	—	—	—	—	—	26
20–24	29	18	23	31	—	—	—	—	—	—	—	26
25–29	39	21	24	29	33	34	—	—	—	—	—	31
30–34	57	27	31	35	38	39	42	42	—	—	—	39
35–39	82	39	40	48	50	51	51	55	62	68	68	52
40–44	113	59	57	59	77	71	72	67	72	71	80	71
45–49	—	—	—	—	—	—	—	—	—	—	—	101
All	40	25	30	38	45	48	52	57	66	70	77	36

for England and Wales in 1939-40, and refer only to single births, it being impossible, from the Registrar-General's tabulations, to include twin and triplet maternities. But the difference that this omission makes to the general picture is negligible. All rates shown are based on at least 80 deaths.

The table shows the following features :

At any given birth-parity, the still-birth rate increases steadily with age of mothers.

At any given maternal age, the rate is highest for the first-born, lowest for the second-born, and then increases slowly with increase in parity.

There are no national figures relating neonatal death-rates to age of mother or birth-parity. But various special studies, including those of Burns (1942) in the County of Durham, of Baird (1945) in Aberdeen, and of Woodbury (1925) in a number of towns in the USA, agree in the conclusion that, at any given maternal age, the pattern of neonatal mortality-rates in relation to birth rank is similar to that for still-births. They also find that mortality-rates are higher for the older mothers, but there is a suggestion that rates may be rather higher for mothers below twenty years of age than for those in the early twenties. It is desirable that the question should be investigated on a large enough scale to give reliable rates in all sub-groups.

Sex Ratio

Male still-births number about 120 for every 100 female still-births. Neonatal mortality-rates among male babies are about 125% of the female rate. But when the total rates are analyzed by cause, curious differences appear. Table VI

TABLE VI. RATIO OF MALE TO FEMALE STILL-BIRTHS, SCOTLAND, 1939-43

	1939	1940	1941	1942	1943	Mean
General diseases in mother	1·08	1·77	1·72	1·13	1·42	1·42
Toxaemias in mother	1·18	1·39	1·58	1·36	1·21	1·34
Ante-partum haemorrhage	1·41	1·24	1·36	1·26	1·36	1·33
Difficult labour	1·68	1·72	1·56	1·61	1·35	1·58
Foetal malformations	0·64	0·69	0·63	0·57	0·60	0·63
Other defined causes	1·19	1·28	1·49	1·23	1·20	1·28
Undefined causes	1·27	1·28	1·28	1·37	1·11	1·26
All causes	1·28	1·26	1·27	1·19	1·11	1·22

gives the ratio of male to female still-births in Scotland in the main cause groups. There is a substantial male excess in all cause groups except foetal malformations, where the female still-births outnumber the male by more than 3 to 2. Male foetuses are more liable than female to succumb to the perils of the process of being born ; but the incidence of lethal defects in the foetus itself is higher among females. The relative sex incidence varies greatly for different kinds of malformations, as is shown in Table VII. The largest single

TABLE VII. STILL-BIRTHS FROM FOETAL MALFORMATIONS, SCOTLAND, 1939-43

	Total	Male	Female	Ratio, male to female
Anencephalus	1,180	325	855	0·38
Hydrocephalus	604	318	286	1·11
Multiple malformations	351	132	219	0·60
Spina bifida	236	95	141	0·67
Others	544	249	295	0·84
Total	2,915	1,119	1,796	0·62

category of malformations, anencephalus, was responsible for 1,180 still-births in the five years in Scotland. The male to female ratio was 0·38. Hydrocephalus showed a slight male excess, but all other kinds of malformation, with two very minor exceptions, predominated in female foetuses.

There is a similar wide variation in the sex incidence of deaths among live-born infants from congenital malformations. This is shown in Table VIII, which is condensed from

TABLE VIII. RATIO OF MALE TO FEMALE DEATHS AMONG LIVE-BORN INFANTS FROM CONGENITAL MALFORMATIONS, ENGLAND AND WALES, 1931-35

Pyloric stenosis	3·88
Imperforate anus	3·07
Cleft palate, hare lip	1·66
Other malformations of digestive tract	1·49
Heart	1·41
Hydrocephalus	1·27
Other malformations of central nervous system	0·83
Other skeletal malformations	0·74
Spina bifida, meningocele	0·70
Monstrosities	0·67
Naevi	0·53

a table given in the annual report of the Registrar-General of England and Wales (text, 1936).

The ratio of male to female deaths varies from 3·88 to 0·53, and in no category is it even approximately unity. It is interesting to note that in the two categories that appear in Tables VII and VIII—hydrocephalus and spina bifida—the sex ratio among still-births is very similar to that among live-births.

Extent of Influence of Social Factors not Apparent from Crude Statistics

Some of the evidence for attributing great influence to social and economic conditions has already been given in Tables II and III. Still-birth rates, and infant mortality from prematurity and the unsatisfactory diagnosis of " congenital debility ", increase steadily from Class I to Class V. The Registrar-General's analysis by social class does not display the full extent of difference in the rates in different sections of the population. The worst county boroughs in England and Wales, for example, show considerably higher still-birth and neonatal death-rates than those for Class V as a whole. Nor do observed differences in rates between social classes express the full effect of economic conditions, because of the class gradient in fertility. The average number of children per family in Class I is less than in Class V. There will therefore be a larger number of first-born per 1,000 births at the higher social level, entailing a bigger mortality risk. Increasing poverty and increasing size of family pull in opposite directions in their effects on still-birth and neonatal death-rates. If one could subdivide the births in Class I and Class V by parity and age of mother, and compare the rates in each sub-group, the contrast would necessarily be greater than that found between the crude figures, which take no account of the differences in biological composition of the social classes with respect to birth parity and age of mother.

Influence of Maternal Nutrition and of Medical Care

There is a consensus of medical opinion, expressed in such articles as that of Young (1945), that still-birth and neonatal rates are greatly influenced by maternal nutrition in the prenatal period. The evidence, which there is no space to consider fully here, is reviewed in a paper shortly to be published by Woolf (1946), and is discussed also by Huggett (1946) in this number. Woolf also subjects the still-birth and neonatal mortality-rates in county boroughs of England and Wales to a process of multiple regression analysis similar to that employed in a published study by Woolf & Waterhouse (1945). He finds that both rates tend to increase with decreasing size of family. When this is allowed for, still-birth rates are very sensitive to increases in the percentage of men unemployed or in low-paid occupations, but are hardly

affected at all by indices of overcrowding. This is consistent with the view that poverty exerts its influence primarily through malnutrition. Among neonatal deaths, the indications are that overcrowding and malnutrition are both of importance. This aetiological differential is supported by changes in the rates during the war. There has been an improvement in nutrition among the poorest section of mothers, due to the abolition of unemployment, the upward levelling of earnings, and the nutritional policy of the Government. On the other hand, housing conditions probably deteriorated. Between 1938 and 1944, still-birth rates dropped from 39·8 to 28·5, a fall of 11·3, but neonatal mortality dropped only by 3·8, from 28·3 to 24·5.

Woolf also gives an account of the evidence that still-birth and neonatal rates can be drastically reduced by improvements in the standards of medical and nursing care. Besides special studies like that of Baird (1945), this proposition is supported by much indirect statistical evidence. It is only by this means that one can account for the very low rates in Greater London, and the abnormally high rates among mining communities, which are still evident when differences in crowding, poverty and size of family are fully taken into account.

In summing up, it is convenient to consider congenital malformations separately from the other categories of still-births and neonatal deaths. The majority of still-births seem to arise from the hazards of the birth process. This must depend greatly on intra-uterine conditions, since the risk varies so much with birth parity and maternal age. There are good grounds for believing that the intra-uterine environment is also adversely affected by maternal malnutrition, and that the hazards of birth can be substantially diminished by antenatal and obstetric care. Neonatal deaths, whether ascribed to prematurity or not, are much more frequent in premature than in full-term infants. The incidence of prematurity can be reduced by improved social conditions, especially nutritional, and by better professional care, which can also prevent many deaths when prematurity has occurred (cf. Crosse, 1945). Death-rates in all these categories could also be reduced by an increase in the average size of family and a decrease in the average maternal age.

Congenital Malformations

Congenital malformations seem to differ from the other categories of still-births and neonatal deaths. Here there seems no basis for sober optimism, nor any indication of a plan for attacking the problem. It seems that such defects arise during the process of fertilization of ovum by spermatozoon, and that nothing we may do afterwards can undo the damage. That may turn out to be the case. But there are some things about congenital malformations that need investigation before this pessimistic conclusion can be accepted. Firstly, there are the curious differences in sex-ratio in the various kinds of malformation. These form a challenge to medical geneticists, and their investigation might well bring to light new facts about human malformations that would provide the basis for preventive action. Secondly, there is some evidence that the death-rate from congenital malformations depends on intra-uterine environment and is not solely determined by gene interactions at fertilization. Apart from the case implicating maternal rubella, discussed elsewhere (Parsons, 1946) in this number, there are the following indications :

TABLE IX. STILL-BIRTHS FROM FOETAL MALFORMATIONS PER 1,000 TOTAL BIRTHS BY MATERNAL AGE, SCOTLAND, 1939-43

Age of mother	1939	1940	1941	1942	1943	Mean
Under 20	4·0	5·5	5·5	5·6	2·9	4·7
20–24	4·1	4·5	5·2	5·6	5·1	4·9
25–29	5·4	5·5	5·5	5·7	4·7	5·4
30–34	6·7	6·2	7·2	7·3	7·0	6·9
35–39	7·8	9·1	9·7	9·2	8·6	8·9
40 and over	9·5	10·8	9·4	11·2	9·5	10·1

1. Deaths from congenital malformations are abnormally high in occupational groups where women do prolonged or heavy work during pregnancy.

2. Deaths from congenital malformations, like other categories of neonatal mortality, are abnormally low in Greater London. Can this be an effect of better antenatal and obstetrical care ?

3. The still-birth rate from congenital malformations varies greatly with age of mother. The figures for Scotland are shown in Table IX. It is difficult to explain the rise in rate with maternal age except as indicating that intra-uterine conditions must have a marked influence on the genesis of foetal deformities.

It is, of course, true that the figures show only death-rates, and not incidence-rates of foetal malformations. It may be that large numbers of foetal monstrosities are aborted early in pregnancy, and that there is a sex difference in abortion rates. It may be that in some cases—e.g. cleft palate—a substantial proportion of affected individuals are viable, and that the sex-ratio among these is different from that among those who succumb. Taking still-births and live-births together, the total loss of infant life from congenital malformations is greater than the combined figure for measles, whooping-cough and diarrhoea and enteritis. The problems briefly touched on here are surely worth a full-scale investigation.

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THE PATHOLOGY OF STILL-BIRTH AND NEONATAL DEATH

A review of 1053 cases

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Recent years have seen an awakening of interest in the problem of neonatal mortality. Pathological studies of the causes of foetal and neonatal death have helped materially to define the extent and nature of the problem, and have revealed certain facts of the greatest importance, which formerly were not appreciated. It has been shown that clinical diagnosis, when unconfirmed by post-mortem findings, is liable to be inaccurate. This is not surprising, as the clinical manifestations, even of grave disease in the newly born, can be extremely obscure and misleading even to the most skilled observers. This is therefore one of the branches of medicine in which the close co-operation of a pathologist can be of the utmost value to clinical workers, and it is regrettable that even now, despite much improvement in recent years, the pathology of still-birth and of the neonatal period is still a somewhat neglected field.

The following brief review of the subject is based on the experience of the writer as pathologist to a large maternity hospital, where it has been the practice for many years to perform necropsies on all live-born babies that die in hospital, except for the very few for which permission is refused by the parents, and also on a large number of dead-born foetuses. The results presented may therefore be accepted as fully representative of the foetal and neonatal mortality of the hospital.

TABLE I. CAUSES OF FOETAL DEATH IN 435 CASES OF STILL-BIRTH

Condition	Full-time	Premature	Total	Per cent.
Developmental defects	23	65	88	20·2
Intracranial haemorrhage	68	37	105	24·1
Asphyxia	94	68	162	37·2
Infections	11	3	14	3·2
Miscellaneous	10	11	21	4·8
Not ascertained	12	51	63	10·3

TABLE II. CAUSES OF 618 NEONATAL DEATHS

Condition	Full-time	Premature	Total	Per cent.
Developmental defects	42	23	65	10·5
Intracranial haemorrhage	31	140	171	27·6
Asphyxia	14	67	81	13·1
Infections	64	126	190	30·7
Miscellaneous	24	25	49	7·9
Prematurity only	—	55	55	9
Not ascertained	7	—	7	1

Table I presents the pathological findings in 435 cases of still-birth, and Table II those in 618 cases of neonatal death, arranged according to what was deemed to be the principal cause of death. From these it is evident that the majority of cases of still-birth fall into one of three main categories—defects of development, asphyxia, and intracranial haemorrhage—while in cases of neonatal death a fourth important group is added—infective diseases. These four categories included over 80% of both still-births and neonatal deaths, and are therefore of such great importance that they must be dealt with in some detail.

Defects of Development

Developmental defects were found in 20% of the still-births and 10·5% of the neonatal deaths. There is a great variety of these conditions that may prove incompatible with the establishment or continuance of independent existence after birth. They are not preventable, and their interest is embryological rather than pathological or clinical. No detailed description of these conditions or discussion of the embryological problems concerning them is appropriate here, but brief mention may be made of some of the commoner forms of maldevelopment.

Congenital cardiac defects are more often a cause of neonatal death than of still-birth. They occur in endless variety. Those that cause death in the neonatal period are often complex and of severe grade. Anencephaly is relatively common as a cause of still-birth. Very occasionally an anencephalic foetus is born alive, but they never survive long. Spina bifida is one of the commonest developmental malformations, most often affecting the lumbo-sacral region, and usually associated with meningocele or meningo-myelocele, and often with congenital hydrocephalus. These infants are most often full-term and born alive. Sometimes in cases of occipital meningo-encephalocele, the whole brain lies outside the cranium, within the sac, and the low, flat vault of the skull, enclosing a tiny cranial cavity, gives an appearance resembling anencephaly. Such infants occasionally survive for several days.

Diaphragmatic defects, with displacement of abdominal organs into the thorax, are less rare than is often thought. They are much commoner on the left side than on the right. The most usual type is the so-called "false hernia," where the pleural and peritoneal sacs are in continuity through the defect in the diaphragm, and the displaced viscera are not enclosed in a hernial sac. Sometimes, however, the two serous cavities are not continuous, and the displaced abdominal viscera have a covering composed of peritoneal and pleural membrane, which separates them from the thoracic organs. In cases of diaphragmatic hernia it is usual to find that the lung on the affected side is imperfectly developed, sometimes vestigeal.

Developmental defects of the urinary system are among those most often encountered. Absence of both kidneys is an occasional cause of early neonatal death. Extreme cases of bilateral renal hypoplasia and of polycystic disease may be incompatible with life beyond a few days or weeks. Congenital hydronephrosis does not often cause death so early, but may be found when death is due to another cause. The writer has been impressed with the frequency with which developmental errors of the genito-urinary system accompany other defects, which may be of a more lethal nature. Thus the pathologist whose work is with newly born infants and

foetuses comes to regard such conditions as absence or extreme hypoplasia of one kidney, horse-shoe kidney, and double ureter or pelvis, as fairly common occurrences, while he whose work is with older subjects regards them as rarities.

Asphyxia

Asphyxia resulting from stress of birth or accidents such as antepartum haemorrhage or prolapse of the cord is among the most important causes of still-birth and neonatal death. It accounted for 37·2% of the still-births and 13·1% of the neonatal deaths in the writer's series. The degree of asphyxia suffered by the foetus may be sufficient to cause death before delivery. Such foetuses will show at autopsy clear signs of asphyxia: multiple subserous petechial haemorrhages, especially in the thorax, haemorrhages in the thymus and lungs, dilatation of the right side of the heart, extreme venous engorgement throughout the body, and dark, fluid blood. In addition, the asphyxiated foetus may have passed meconium into the liquor amnii and inhaled it. The colon will then be found empty, and the respiratory passages full of greenish fluid, the lungs being sometimes so full that they are to some extent expanded, and are bulky and heavy like pneumonic lungs, and of a green tint.

More commonly, without passage of meconium, asphyxia may stimulate the foetal respiratory centre so that attempts at respiration are made before the child is born, with the result that the lungs are flooded with liquor amnii. This can be recognized under the microscope by the presence of solid debris, which is suspended in the liquor amnii. Cornified cells, lanugo hairs, and masses of vernix caseosa, all derived from the skin of the foetus, are found in large quantity in the lungs.

Although there is some difference of opinion as to whether any liquor amnii normally enters the foetal lungs, there is little doubt that any considerable quantity is abnormal and indicates severe foetal asphyxia. This is a common finding both in still-births and in asphyxiated infants that are born alive. In the latter, the water-logged state of the lungs interferes seriously with the establishment of respiration, and the presence of so much solid material may, of itself, prevent proper aeration. Especially is this the case when the foetus has inhaled masses of vernix. This material, when found in unaerated lungs, is in solid lumps, but, when air enters, the vernix becomes plastered against the walls of the air-spaces as a membrane, which may form a complete lining in bronchioles, alveolar ducts and alveoli. This causes most serious obstruction to the passage of air, and is usually accompanied by extreme atelectasis, while areas of lung into which air does enter may become over-inflated, producing acute emphysema, which is often of interstitial type: air bullae form in the interlobular septa and pleura, and the rupture of subpleural bullae is an occasional cause of spontaneous pneumothorax in the newly born.

Asphyxiated infants suffer, not only from mechanical effects of inhaled liquor amnii, but from depressed activity of the respiratory centre, which is the direct result of asphyxia when it reaches the degree at which stimulation is succeeded by depression or paralysis. Such infants do not cry well and may continue for some hours, or even a day or two, with shallow breathing which never adequately expands the lungs. If an infant remains in this condition until death, the lungs are found in a state of almost complete atelectasis. They may be macroscopically indistinguishable from the lungs of a foetus that has never breathed, and they sink heavily in water. Microscopical examination reveals that air has penetrated only to some of the bronchioles and alveolar ducts, and there may be no aeration of alveoli. This condition may be found in an infant that has lived as long as 24 hours. If an infant continues thus into the second or third day, the lungs almost inevitably develop an increasing oedema, and, as will be seen later, are very prone to become the seat of pneumonia.

The extreme venous engorgement that accompanies asphyxia may be a cause of severe and fatal haemorrhage at various sites, to which reference will be made later.

Intracranial Haemorrhage

Intracranial haemorrhage was responsible for 24·1% of the still-births and 27·6% of the neonatal deaths in the writer's series of cases. Three distinct types are common: subdural, subarachnoid, and intraventricular.

Subdural haemorrhage is perhaps the most familiar. It results directly from birth trauma that causes tearing of intracranial veins. The commonest site of injury is the tentorium cerebelli. Especially when the free margin is damaged, a vein is liable to be torn across and free haemorrhage into the subdural space results. Less often, the falx cerebri is the site of the tear, which may cause severe haemorrhage if the inferior sagittal sinus is involved. An occasional cause of very severe haemorrhage is rupture of the great cerebral vein, usually close to its point of entry into the straight sinus (sinus rectus). Subdural haemorrhage is apt to occur under circumstances that cause excessive moulding or compression of the foetal head: disproportion, obstructed labour from various causes, and intrumental deliveries. It is to be expected that a majority of cases should be in full-term babies, and this is the case; but it is noteworthy that the number of cases in premature infants is large in proportion to the number of premature births.

Subarachnoid haemorrhage is less important, though it is a frequent finding in both still-births and neonatal deaths. Except when it is secondary to intraventricular haemorrhage, the bleeding comes from veins in the leptomeninx over the surface of the brain. It is considerably commoner in premature than in full-term infants, and, as evidence of severe asphyxia is usually present, and there is often a history of some condition such as antepartum haemorrhage, which would be likely to cause foetal asphyxia, the haemorrhage can usually be explained as a result of asphyxial venous engorgement. Under these conditions, haemorrhage is probably more likely to result in the premature, owing to the immaturity of the veins, in which the muscle and elastic tissue are not fully developed. Subarachnoid haemorrhage is not often very severe, and is probably seldom in itself a direct cause of death. Blood effused in this situation is readily absorbed, and there is little risk that it will become organized. There is therefore no reason to suppose that it often produces permanent harmful effects, though the writer has seen hydrocephalus result from organization of a subarachnoid haemorrhage at the base of the brain.

Intraventricular haemorrhage is much more deadly. It is of interest in that it is almost entirely a disease of the premature. In a consecutive series of 156 cases of intraventricular haemorrhage examined by the writer, only 7 were

in full-term babies. It is not very often found in still-births (only 19 of the 156 cases were still-births); it is most frequent in live-born infants that die on the first day; and although it may be encountered late in the neonatal period, it is rather uncommon after the first week. The source of the haemorrhage is usually a vein in the floor of one of the lateral ventricles, most often the terminal vein, which runs in the groove between the thalamus and the caudate nucleus. Haemorrhage occurs first under the ependyma. If this ruptures, free bleeding takes place into the ventricles. Sometimes the source of the haemorrhage is the choroid plexus. In a severe case, the whole ventricular cavity may be filled with blood-clot, which forms a complete cast of all the entriclesv and aqueduct. As some blood usually escapes into the subarachnoid space, intraventricular haemorrhage is usually accompanied by subarachnoid haemorrhage. It may cause a great increase of intracranial pressure, and it is probably rapidly fatal in most cases. At necropsy, there is usually evidence of asphyxia at birth, but there may be other aetiological factors not as yet understood. It is probable that the haemorrhage into the ventricles does not usually occur until a variable time after birth, but it may be that the subependymal haemorrhage takes place as a result of birth-asphyxia, the rupture through the ependyma being delayed for some hours or days.

A less common type of haemorrhage, sometimes associated with intraventricular haemorrhage, is when bleeding occurs into the brain-substance in the central part of the cerebrum. Sometimes this is associated with thrombosis of the choroidal and great cerebral veins.

Another infrequently-encountered type of intracranial haemorrhage is extra-dural, which is the result of severe trauma, with rupture of sutures or fracture of the parietal bone, when the most probable source is injury to the middle meningeal artery.

Infective Diseases

Perhaps the most valuable contribution that pathology has made to knowledge of disease in the newly born is the revelation of the immense importance of infection as a cause of neonatal death.

TABLE III. CAUSES OF 241 NEONATAL DEATHS AFTER THE THIRD DAY

Condition	Number	Per cent.
Developmental defects	20	8·3
Intracranial haemorrhage	22	9·1
Asphyxia	1	0·4
Infections	158	65·5
Miscellaneous	40	16·6

Infection was responsible for 3·2% of the foetal deaths and 30·7% of the neonatal deaths in the writer's series. Table III, which deals with the same series of cases as Table II, but excludes all deaths in the first 3 days, reveals that among those babies that survived the immediate risks of birth, and died during the first month, almost two-thirds died of infective diseases. This is a fact that would have been thought incredible a few years ago, when less was known about these matters, and even yet it is not appreciated as it should be. The importance of this fact cannot be exaggerated, for it is in this group that most improvement in mortality may be anticipated as a result of preventive measures.

Respiratory Infections

The common lethal infections are those of the respiratory tract, especially pneumonia, and those of the alimentary tract, including neonatal gastro-enteritis and severe thrush affecting the oesophagus and sometimes the stomach and intestine. Of these, much the most common is pneumonia. This has some forms that are peculiar to the neonatal period, and some that are commoner then than at other ages.

In the first week, and especially in the first three days, pneumonia usually affects lungs in which an abnormal condition has developed as a result of birth-stress. As has already been said, lungs that are atelectatic, oedematous, or filled with liquor amnii as a result of birth-asphyxia, are very prone to develop pneumonia, infection being contracted either during birth from the maternal passages, or after birth from the environment. In pneumonia of this type, consolidation is seldom massive and its presence is masked by atelectasis and oedema. It is therefore easily missed at necropsy, though the experienced pathologist will usually detect an altered consistence by which its presence may be suspected even when it is not visible to the eye. Microscopical examination reveals pneumonia in many cases in which it is not detected at necropsy.

In the later weeks of the neonatal period, pneumonia is seen in forms that occur also in older infants. Typical bronchopneumonia tends to be massively confluent. As in older infants, it may be caused by the common pathogens of the respiratory tract—*Strep. haemolyticus*, *Pneumococcus*, *H. influenzae*—but cases that are typical pathologically may be due to infection with organisms that do not have such effects in older subjects, notably those of the *B. coli* group. This is an interesting feature of other neonatal infections besides pneumonia.

Two other types of pneumonia must be mentioned because, though not confined to the neonatal period, they are commoner then than at a later age. Septic aspiration pneumonia, due to inhalation of milk or, more often, of regurgitated or vomited gastric contents, produces widespread consolidation with haemorrhage and a purulent type of exudate, among which are found masses of aspirated foreign material and bacteria; and the action of the gastric juice, causing lysis of blood and digestion of tissue, gives the microscopical picture easily recognized characters. It should be emphasized that this is a common type of neonatal pneumonia. The other special type is staphylococcal pneumonia. This is essentially a disease of infancy, and it is relatively common in the newborn. It may be caused by inhalation of milk containing *Staph. aureus*, but not all cases can be so explained; some result from infection transferred from the baby's environment, from the attendants or other babies in the nursery. Cases occur sometimes in association with outbreaks of other types of staphylococcal infection in hospital nurseries. The condition affects one or more large areas of the lung. Suppuration develops rapidly in the bronchi and spreads to the alveolar tissue; multiple abscesses form, and the part undergoes complete disorganisation. Empyema and pyo-pneumothorax follow the rupture of abscesses into the pleural cavity. Death supervenes after an illness of a few days.

Alimentary-tract Infections

Neonatal gastro-enteritis is an epidemic disease that presents a grave problem in institutions. The bacterial cause

is unknown, despite much investigation. No known intestinal pathogen has been incriminated. Certain evidence points to a virus as the cause. Evidence that it may be secondary to a parenteral infection is less satisfactory than in the case of gastro-enteritis in older infants. The pathology is somewhat indefinite. Sometimes little is found apart from wasting and dehydration. But in many cases there is some evidence of an inflammatory condition, with severe congestion in the stomach and upper jejunum, sometimes with slight haemorrhage from the congested mucosa. Ulceration does not develop. In some cases the liver is enlarged and fatty, but this is not constant. In many cases a terminal pneumonia develops, often of the septic aspiration type, from inhalation of vomitus.

Thrush not uncommonly assumes a severe and dangerous form in the newly born, when the infection spreads from the mouth to the pharynx and oesophagus, less often to the stomach, and occasionally to the intestine. The thrush organism (*Monilia albicans*) forms masses, which adhere to the mucous surface as large flat plaques or small, sharply-defined raised nodules. The mucous surface under these is ulcerated to a varying depth; mycelium of the organisms may penetrate deeply into the wall of the organ. The amount of inflammatory infiltration varies, and is sometimes not great. Oesophageal thrush is a dangerous condition. The infants die of inanition or from septic aspiration pneumonia.

Other Infections

Other types of infection were relatively uncommon in the series of cases under consideration. Septicaemia and pyaemia from umbilical sepsis, skin infections, or other source, occasionally occurred. There were several cases of meningitis, due to the pyogenic cocci or to *B. coli*. This is another example of the unusual pathogenic effects of *B. coli* in the newborn. The writer has a record of only one fatal case of osteomyelitis, which ended in pyaemia. Renal infections are rarely fatal in the neonatal period. Congenital syphilis caused a small number of still-births but very few neonatal deaths. Its small part in the mortality is a tribute to efficient treatment of the mothers. It is the writer's experience that, if a syphilitic infant is born alive, it usually survives the neonatal period.

Miscellaneous Conditions

The most important of the various conditions that were included under this heading in the tables is haemolytic disease of the foetus and newborn (erythroblastosis foetalis). This disease has aroused much interest in recent years, since its cause was discovered in incompatibility of the blood of mother and foetus in respect of the Rhesus factor, which accounts for the vast majority of cases. Reference to this subject[1] must here be confined to brief mention of the various pathological types of the disease.

The least severe form, not often fatal, is anaemia haemolytica neonatorum, in which a severe haemolytic anaemia, without jaundice, develops soon after birth. The commonest form is icterus gravis neonatorum, in which jaundice develops at or soon after birth, becomes deep, and is associated with severe anaemia, and sometimes with cerebral symptoms referable to an associated "kernicterus", in which nerve-cells in certain nuclei of the brain undergo degeneration and become deeply bile-stained. Such cases are often fatal in the early days of life, but some of the infants recover. More severe, invariably fatal, and usually a cause of still-birth rather than of neonatal death, is hydrops foetalis, in which a very severe general oedema is associated with profound anaemia, but usually no jaundice. These are the three well-recognized forms of the disease. But a fourth, and most severe, form occurs, which causes earlier intra-uterine death. The foetus is macerated when born and may not be hydropic.

All types have certain features in common: spleno- and hepato-megaly, with excessive extra-medullary haemopoiesis in the liver, spleen and elsewhere; excessive haemosiderin deposits in the liver and spleen; and a characteristic blood-picture, with abnormally numerous nucleated red cells, many of a primitive type, with corresponding changes in the bone-marrow. In the case of a macerated foetus, the characteristic blood-picture and other evidence of erythroblastosis may not be recognizable. In some of the more-severe cases, especially of hydrops, central-zone necrosis in the liver may be found, sometimes with an early replacement-fibrosis. In the type with maceration, this may have proceeded to a stage of diffuse fine fibrosis, which presents a picture so like that of congenital syphilis that many cases must undoubtedly have been ascribed to that disease, especially as there is usually a similar family history of repeated still-births. The principal distinguishing features between the two diseases are the presence of heavy haemosiderin deposits in the liver and the absence of spirochaetes in haemolytic disease, and the reverse in syphilis; and the results of serological tests for syphilis and of tests for the Rhesus factor and antibodies.

Other conditions that can only be mentioned among those included in the "Miscellaneous" group are haemorrhage in the suprarenal glands, in the peritoneal sac (usually from rupture of a subcapsular haematoma on the surface of the liver), in the lungs, and from acute ulcers in the duodenum or at the lower end of the oesophagus; obstructive lesions of the bowel other than those of developmental origin, most often volvulus of the small intestine; and rare cases of neoplasm.

Prematurity

One fact that emerges clearly from this study is the outstanding importance of prematurity as a factor in foetal, and more especially in neonatal, mortality. The figures given in Tables I and II show that 54% of the still-births and 70·5% of the neonatal deaths were in cases of premature birth. During the period covered by this series of cases, slightly over 10% of all live-births in the hospital were premature; and it was this 10% that produced almost three-quarters of the neonatal mortality. Except when it is extreme, prematurity is seldom the sole ascertainable cause of death, but its importance as a factor predisposing to death from almost every other cause cannot be exaggerated. In this series, among the live-born infants that died of asphyxia, 82·7% were premature; of those that died of intra-cranial haemorrhage, 81·8%; and of those that died of infection, 66·3%. This shows how close the problem of neonatal mortality is to that of prematurity; for nothing could make a greater contribution to a reduction in the neonatal deathrate than prevention of premature births.

Summary

Of 435 cases of still-birth and 618 of neonatal death, the majority of the cases fell into one of four main pathological

[1] [See paper in this number by R. R. Race (*BMB* 872).—Ed.]

groups—defects of development, asphyxia, intra-cranial haemorrhage, and infective diseases. A brief description of the principal pathological features of each of these is given.

Mention is made of various less common conditions that were included in the series, notably haemolytic disease of the foetus.

The importance of prematurity as a factor in neonatal mortality is emphasized.

THE POST-MORTEM EXAMINATION OF THE NEWBORN INFANT

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The high mortality-rate of newborn infants is in striking contrast to the magnificent achievements of preventive medicine in reducing the mortality of later infancy. "The slight improvement in neonatal mortality in the last 30-40 years is due almost entirely to a reduction in the deaths in the last three weeks of the neonatal period" (Parsons, 1944). Any progress in this realm of medicine can be expected only from an accumulation of thorough knowledge of the physiology and pathology of intra-uterine life (Parsons, 1946), of the act of birth, and the transition from intra-uterine to extra-uterine life. The morbid anatomy of the neonatal period is an essential part of this science.

There is no unanimously accepted definition of the newborn infant. The frequently-adopted limit of 4 weeks is arbitrary. There are more differences between the pathology of the 1st week of life and that of the 3rd or 4th than between the latter and the 8th or 10th week. The first three months of extra-uterine life are on the other hand the most dangerous period of infancy, peculiar by the poor reaction to artificial feeding, low resistance to infections, and hydrolability. For this reason the designation "neonatal period" will be used in this paper as synonymous with the first three months of life, and the first week of life will be separated as the "early neonatal period."

A discussion of the pathology of the newborn infant is beyond the scope of a short article. The present paper will therefore be restricted to the description of a comparatively simple technique, which appears satisfactory to the writer, for the post-mortem examination of the newborn infant, drawing attention at the same time to frequent or interesting findings and their interpretation. We have, however, to realize that there is no post-mortem technique which can be dogmatically applied to every case. Each autopsy is a piece of individual research work, and the pathologist is often confronted with findings which demand a special technique.

I. EXTERNAL EXAMINATION

The body should be inspected thoroughly for the presence of external abnormalities or injuries, cyanosis or icteric discoloration, abundance and distribution of lanugo hairs, the configuration of the head, the direction of p alpebra fissures, the presence of epicanthus, the ocular distance, the configuration of the small finger, the presence of oedema, scleroedema, sclerema or adiponecrosis subcutanea neonatorum.

The last three conditions are often confused. In scleroedema there is a hard pitting swelling of the skin. and the impression of the finger disappears slowly. In sclerema, which is much rarer, the skin appears shrunken, is even harder, like wood, and pitting is absent or minimal. Adiponecrosis neonatorum is sometimes called scleroderma neonatorum or pseudosclerema. It is a sharply-demarcated local lesion of the skin, pale reddish or bluish in colour, traumatic in origin. Calcification and foreign-body giant-cells may be found on histological examination. Slight oedema is very frequent in the newborn infant. Marked oedema associated with pneumonia of the newborn has been repeatedly seen by the writer. Gross oedema associated with a large oedematous placenta should draw attention to hydrops foetalis, and the diagnosis should be checked by histological examination and serological tests on mother and baby. Post-mortem blood gives, however, reliable results in Rh tests only within a few hours after death.

The umbilicus and the skin deserve special attention. If the stump of the umbilical cord has fallen off and any exudate or membranes are present, these should be examined bacteriologically. In every case with trismus or tetanic cramps, the stump of the umbilical cord should be minced and ground with sterile Tyrode's solution or, in the absence of a stump, scrapings of the umbilical wound should be suspended in Tyrode's solution. A part of such a suspension should be used for anaerobic cultures, the remainder being injected subcutaneously into a mouse. "Stumps" more often give positive results for tetanus than "scrapings".

If large vesicles are present in the skin, or/and in large areas—especially on the face—the epidermis is separated from the corium, gentle pressure by the finger should be applied to an apparently normal area of the skin. An artificial separation of the epidermis (phenomenon of epidermolysis) is pathognomonic for Ritter's disease if the post-mortem examination is done shortly after death. Pustules and vesicles are the common form of skin infection in the early neonatal period, while deeper abscesses, so common in marasmic babies of later infancy, are rare at this age. The skin of the face should be inspected for the presence of diffuse syphilitic infiltrations and the "café au lait" colour, the lips for fissures, the palms of the hands and the plantar surfaces of the feet for diffuse desquamating infiltrations or syphilitic pemphigus. The latter is present at or appears immediately after birth and is seen only in the early neonatal period.

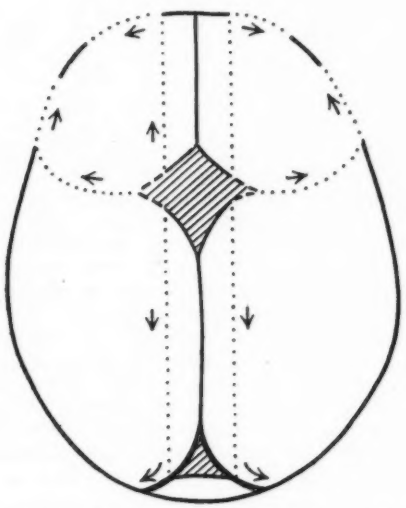
Before starting with the necropsy the mouth should always be inspected for the presence of Bednar's aphthae—

superficial ulcerations in the regions of the raphe palati and pterygoid processes—for thrush and for swelling of the alveolar processes. The latter, which is sometimes seen in young infants and may be associated with necrotic or gangrenous changes of the gingiva, is a septic process which is characteristic of the neonatal period. It was first described by Klementowsky (1876) as osteogingivitis gangraenosa, and its pathology was studied by Zarfl (1920). It is a haematogenous infection of the tooth-bud leading progressively to an osteomyelitis of the jaw, sequestration of the bud, and sometimes gangrene of the gingiva (Fischl, 1931).

II. HEAD AND SPINAL CORD

The dissection of the head begins with the usual ear-to-ear incision, the two flaps being pulled forwards and backwards respectively and inspected for haemorrhages, serous or blood-stained fluid. The bones of the vault should then be examined for subperiosteal haematomata and fractures. The vertex of the brain is exposed without damage to the superior longitudinal sinus or the inflowing pial veins, by forming and turning down flaps consisting of the two parietal bones and the lateral halves of the frontal squama, according to the following technique: an incision is made with a pointed knife into the anterior fontanelle at its posterior margin, approximately 5 mm. from the midline. The point of the knife is pushed parallel to the inner aspect of the parietal bone for 1-2 mm. between dura and leptomeninges and the incision is extended to the lateral angle. In a similar way the opposite side and both anterior margins are incised. One blade of a pair of strong scissors is passed beneath the parietal dura at the medial end of the original incision and the parietal bone is cut longitudinally parallel to the sagittal suture and about 5 mm. laterally to the latter. The incision is continued towards the lambdoid suture, and then laterally and downwards within the latter and finally in a similar way

FIG. 1



Schematic drawing illustrating the technique for opening the skull of a newborn infant.
— — — — Primary incisions into the anterior fontanelle made with a pointed knife.
. . . . . Extensions made with a pair of strong scissors.

in the coronal suture. The same procedure is applied to the other side and the two parieto-temporal flaps are turned outward. In the same way flaps of the two halves of the frontal squama are prepared and turned outward. It is usually necessary to make a horizontal fronto-medial extension with the help of a bone-forceps, leaving only a short bridge for outward reflection of the flaps. The procedure, which leaves a medial strip approximately 1 cm. in width with the intact superior longitudinal sinus, is illustrated schematically in Fig. 1.

After reflecting the four flaps, the vertex of the brain, the terminations of pial veins into the superior longitudinal sinus, and—after a gentle sideward pushing of the hemispheres—the falx cerebri, can be easily inspected. Subdural haematomata over the vertex and rupture of pial veins close to their termination at the superior longitudinal sinus are not uncommon, especially in forceps delivery, and are due to kinking of the veins as a result of bitemporal compression and shifting of the parietal bones one over the other (Beneke, 1910). They may, however, occur in spontaneous delivery as a result of a disproportion between the size of the head and the width of the birth-canal. They are more common than is generally assumed, and they are by no means always fatal. Evidence for this statement is the frequent finding of haematogenous pigment on the interior aspect of the dura in later infancy. It is the writer's opinion that such not-immediately-fatal subdural haematomata are a frequent cause of feeding difficulties in the neonatal period. Their relationship to true pachymeningitis haemorrhagica interna, with parallel layers of spiderweb-like membranes, giant capillaries and accumulation of blood-stained or xanthochromic fluid, is a debatable problem.

Subarachnoid haemorrhages are the most common type of intracranial haemorrhage in immature babies, and are often associated with haemorrhagic oedema of the leptomeninges. Most of our knowledge concerning intracranial haemorrhages of immature infants is due to the work of Ylppö (1919, 1924).

After the vertex has been examined, the falx cerebri can be exposed by gentle sideways pushing of the cerebral hemispheres. Haematomata between the falx and the medial aspect of the hemispheres often accompany subdural haematomata over the vertex. Haematomata of varying size between the two dural layers of the falx are often found but, by themselves, without pathological significance. After inspection of the falx, the superior longitudinal sinus is opened and examined for thrombosis and post-mortem or terminal clots. Absence of clots in all sinuses of the dura mater, in the heart, and in the great vessels, associated with manifestations of haemorrhagic diathesis, is suggestive of congenital afibrinogenia (Allibone & Baar, 1943; Henderson, Donaldson & Scarborough, 1945). A definite diagnosis is, however, not permissible without knowledge of *intra vitam* laboratory findings. The possibility of post-mortem fibrinolysis or of asphyxia must be taken into account.

The next step in the examination is the separation of the falx at its antero-inferior insertion. This is then pulled backwards, the cerebral hemispheres are carefully pushed apart, and the corpus callosum is dissected longitudinally, exposing the superior tela chorioidea. A preliminary inspection of the galenic veins is now made. Engorgement of these veins always suggests the presence of haemorrhages. A haematoma may be seen around one or both veins of Galen (vena cerebr

interna), and a rupture may be found near the point where they join the vena magna galeni. The frontal lobes are now raised, the olfactory tracts, the II-VI cranial nerves are cut transversally, and a horizontal cut is made through the pons varolii at the level of the incissura tentorii. The brain can then be removed, leaving the cerebellum, the medulla, and part of the pons in the posterior cranial fossa. The intact tentorium and the base of the skull are then inspected. Tentorial tears are caused by traction mainly due to bi-temporal or suboccipitobregmatic compression (Beneke, 1910; Holland, 1937). Clotted and unclotted blood may be found on the superior aspect of the tentorium and in the posterior cranial fossa. The main localization of tentorial tears is in the superior lamina. They are usually superficial, have ragged irregular margins, and can be easily overlooked. Fissures along the incissura tentorii are much rarer, but probably always fatal because of the massive haemorrhage into the posterior cranial fossa with compression of the medulla. The same is true for tears of the inferior lamina and those through both layers. Haematomata between the two laminae, varying in size from a lentil to a pea, are very frequent, and *per se* without pathological significance, like similar haematomata of the falx cerebri.

The tentorium is now incised along its insertion in the superior border of the petrous portion of the temporal bone, opening at the same time the superior petrosal sinus, and the incision is extended to the anterior part of the occipital insertion. The cranial nerves VII-XII are severed, the medulla is incised with a bistoury as deeply as possible, and the contents of the posterior cranial fossa are removed. The sinuses of the dura mater are opened and inspected, and the pituitary is removed without being touched by an instrument. This is done by making an arched incision along the anterior margin of the diaphragma sellae, grasping one of the posterior clinoid processes with a dented forceps, pushing the knife beneath the pituitary, and cutting through the cartilaginous dorsum sellae. The sella is inspected for remnants of the cranio-pharyngeal duct, which, if present, is found anteriorly, in or just behind the plane of the anterior clinoid processes. The dura of the middle cranial fossa is separated from the bone by means of a chisel and the middle ears are opened, the chisel being thoroughly clean and applied with as little inclination as possible. Slightly blood-stained serous or mucous exudate is very often (about 75%) found in the middle ears in the early neonatal period. This exudate is often sterile and is evidence of an aseptic foreign-body otitis media due to aspiration through the Eustachian tube. If the exudate becomes infected, a purulent otitis media may develop in the early days of life. The exudate is always present in the mastoid antrum as well as in the tympanic cavity. In rare instances the aspirated material contains tubercle bacilli, and this results in a primary tuberculous complex of the middle ear with extensive and uniform caseation of the lymph-nodes in the deep superior cervical group (Baar & Evans, 1941).

The sphenoid, maxillary and frontal sinuses, the ethmoidal cells, the nasal mucosa and the nasopharynx are inspected after a saw-cut in the coronal plane, approximately halfway between the sphenoid limbus and the ethnoidal spine. The angle of inclination of the clivus is measured, and the spheno-occipital and intersphenoid synchondroses are examined whenever a depression of the bridge of the nose is found (achondroplasia, cretinism, etc.). The wings of the sphenoid should be examined when hypertelorism is suspected.

The brain previously removed is now examined further. The roof of the third ventricle is dissected, the pineal gland inspected, and a horizontal section with a brain knife is made through each cerebral hemisphere in such a way that the floors of the lateral ventricles are exposed.

The condition of the veins of Galen, the veins of the corpus striatum and choroid plexus, venae cerebri internae, venae terminales, venae ventriculi lateralis and plexus choroidei is of particular importance. They may be ruptured, and a gross intraventricular haemorrhage may be found, or they may be engorged with punctate haemorrhages in the grey matter surrounding the ventricles. Subependymal haemorrhages are often found on microscopical examination. The pathology of haemorrhages in the galenic system has been thoroughly studied and their mechanism elucidated in a fairly convincing manner by the classic work of Schwarz (1927) in Frankfurt.

According to Schwarz a suction-mechanism is responsible for the majority of intracranial haemorrhages. As soon as the head exchanges the high intra-uterine pressure for the lower atmospheric pressure, a negative pressure is applied to it causing not only a caput succedaneum but also intracranial haemorrhages by propagation through the less-resistant parts of the skull to the sinuses of the dura mater, in particular to the sinus rectus and then to the vena magna Galeni and its tributaries in the galenic system (" caisson mechanism "). A similar mechanism may operate in breech deliveries as a result of rapidly-changing intra-uterine pressure. Schwarz's work has been challenged by some authors, and certainly his ideas are somewhat one-sided. For instance, engorgement and rupture of the veins of Galen may be due in some cases to their being kinked (Holland, 1937), asphyxial haemorrhages are often indistinguishable from those by suction-mechanism, and micronecroses and Virchow's "encephalitis interstitialis neonatorum " (1867) may result not only from birth injury but also from septic infections and from kernicterus (Ceelen, 1920; Baar, 1937). Moreover, physiological reflexes of the newborn, hypertonicity and extensor plantar reflexes, which Schwarz attributed to intracranial haemorrhages, are more reasonably explained by the immaturity of the central nervous system (Reuss, 1931).

Nevertheless, for the majority of cases, the theory of Schwarz appears to the writer to be correct. His theory is supported by the engorgement involving the vena magna galeni and the sinus rectus, by the association with caput succedaneum, by the association of subependymal haemorrhages with clusters of compound granule cells in areas of rarefaction and with perivascular crescents. Intracranial haemorrhage and traumatic necrosis are also responsible for the majority of cases of encephaloclastic porencephaly (Jakovlev, 1941) (=pseudoporencephaly=central porencephaly=cystic degeneration of brain) (Benda, 1945), and of Vogt's status marmoratus of basal ganglia. Encephaloclastic porencephaly is much more common than true developmental porencephaly. (Fig. 3)

At this stage of the post-mortem examination, kernicterus can often be diagnosed. The beautiful golden-yellow spotty discoloration of the thalamus and corpus striatum, especially of the circular cut surface of the tail of the caudate nucleus, are striking findings. These are, however, not the most

frequent localizations. Kernicterus may be present without discoloration of the thalamus and corpus striatum. The examination of the nucleus ruber, corpus luysi and inferior olives is, however, better postponed until the brain has been properly fixed, otherwise no satisfactory histological examination can be performed. It is also worth mentioning that removal of any blood from the cut surfaces of the brain should be done with a clean dry knife, and never with running water. The latter procedure produces marked changes in the nerve cells, and the demonstration of intracellular neurofibrils is rendered impossible (Nissl's " Wasserschaden "). After 3-4 days' fixation the brain is dissected by coronal sections into a series of slices about 5 mm. in thickness. The important nucleus ruber is best seen in the section just anteriorly to the superior corpora quadrigemina. Material should always be set aside for paraffin and for frozen sections. Fixation of the whole brain before any dissection has been performed is often advisable, while injection of formol saline into the internal carotid 12-24 hours before the post-mortem examination is only exceptionally justified in the neonatal period.

Kernicterus is in the vast majority of cases due to icterus gravis neonatorum. Three cases of kernicterus without haemolytic disease, reported in the pre-Rh era, have been recently questioned (Gilmour, 1944). The writer saw one case of kernicterus in which haemolytic disease of the newborn was excluded by haematological and serological investigations. In addition, in one case with haemorrhagic necroses of the liver, histological changes were found in the brain of the same type as in kernicterus. From these observations, based on the histological study of a dozen cases with kernicterus and haematological findings, the conclusion was reached that kernicterus is a hepatogenic encephalopathy, the hepatic disease being in most cases the result of the action of Rh antibodies on the cellular antigens of the liver (Baar, 1945).

Virchow's encephalitis interstitialis neonatorum is a fairly common finding in brains of newborn infants. It is not a distinct pathogenic entity, as it is found in birth-injury, in septic infections, and in haemolytic disease of the newborn. It is usually recognized on histological examination only. Sometimes, however, a peculiar greyish-red colour is noticed in the white matter, which Virchow compared with that of hortensia. Histologically, the most marked changes are found beneath the ependyma of the posterior horns of the lateral ventricles. A perivascular crescent in a case of " encephalitis interstitialis neonatorum " is seen in Fig. 4.

Purulent leptomeningitis is not uncommon in the neonatal period. It is usually caused by *B. coli*, more rarely by *Klebsilla friedländeri* (*Bacillus mucosa*). Unusual strains of *B. coli* as causative organism of leptomeningitis were found at the Children's Hospital, Birmingham, on two occasions, once a *B. coli anaerogenes* which was positive by the methyl-red and Voges-Proskauer tests, and once a strain which resembled biochemically *E. freundi*. Associated with purulent leptomeningitis or without it, there may be found a septic encephalitis which usually takes a necrotizing-haemorrhagic form, abscess formation being rare.

For the findings in the rare Toxoplasma encephalitis of newborn infants, the monograph of Sabin (1942) should be consulted. An infective encephalitis of the newborn resembling toxoplasmosis with coarse subependymal granulations (Fig. 5) has recently been described by Parsons & Baar (1945).

The spinal cord is often neglected in the post-mortem examination of the newborn baby. It is easily exposed by using bone forceps. When being removed it should be held by the cauda equina or the terminal end of the dura without being touched during the whole procedure. Epidural haematomata are found mainly in immature infants, subdural and cord haemorrhages in full-term infants.

III. NECK, THORAX, AND ABDOMEN

For the dissection of the neck, the thoracic and abdominal organs, only the " en masse " technique, after thorough inspection *in situ*, is advisable. The following is a slight modification and combination of directions given by Virchow, Rokitansky, Ghon and Rössle. An antero-median incision is made from the middle of the neck down to the symphysis pubis passing to the left of the umbilicus. After the abdominal cavity has been opened in the whole length of the incision, the skin is separated from the deeper structures of the neck and the thoracic wall, exposing the ribs and costochondral junctions with their periosteum and perichondrium intact. The peritoneum is now inspected and samples of any exudate present are taken for bacteriological examination. The umbilical vein and arteries are examined, the first by a longitudinal slit with small scissors, the latter by a series of cross-sections. Umbilical infection, one of the most important sources of neonatal sepsis, may be present without obvious external involvement of the umbilicus. Macroscopically-recognizable thrombophlebitis umbilicalis is rare, although it may be revealed by histological examination (Morrison, 1944). Umbilical arteries may show a purulent periarteritis, thrombarteritis or a combination of both, the first being in the writer's experience the most frequent.

The gastro-intestinal tract is examined by inspection and palpation for the presence of malrotation, free common mesentery, atresias, the presence of Meckel's diverticulum or persisting vitelline duct, diaphragmatic hernia, *intra vitam* or terminal intussusception, etc. Palpation of the pylorus is very important. A hard hypertrophic pylorus may be found in the early neonatal period before any clinical symptoms have arisen. Dilatation of the duodenum indicates a duodenal stenosis, and is in the majority of cases due either to true obliteration (infrapapillary more often than suprapapillary) or to a torsion as a result of a persisting common mesentery. The latter condition is almost always associated with some malrotation of the gut. Stenoses due to peritoneal bands or abnormal blood-vessels are rare. Multiple atresias of the intestine are not uncommon and usually associated with wedge-shaped defects of the mesentery. After this inspection a decision whether the intestine should be removed separately or included in the " en masse " removal can be made. The latter procedure is always indicated in the presence of atresia ani for the investigation of recto-vaginal, recto-urethral or recto-vesical fistulae, and also in the presence of a thrombosis of mesenteric veins. If the former procedure is decided, the transverse mesocolon is dissected first along its posterior insertion, the descending colon is separated from the abdominal wall, the sigmoid mesocolon is dissected, the rectum freed, transected at the anus and lifted upwards. The dissection is continued downwards from the flexura hepatica, separating ascending colon and caecum or cutting through their mesocolon if such be present. The whole intestine is now lifted and the mesentery of the small intestine is divided with scissors from the ileo-caecal junction medial and upwards

towards the flexura duodeno-jejunalis. The upper end of the jejunum is twice ligated and cut between the ligatures. The sternum is removed by cutting with a cartilage-knife on each side approximately midway between the sternum and the costochondral junctions from the second rib downwards, continuing the incision in an arched way towards the costal margin. The diaphragm is incised and the sternum is separated from the areolar tissue of the anterior mediastinum by raising the xyphoid end of the sternum and dissecting upwards with a knife as close to the bone as possible. The cartilages of the first ribs are divided and the sternum is finally freed by passing the blade of the knife through the sterno-clavicular articulations. The pleural cavities are inspected and samples of any exudate are taken for bacteriological examination. A fibrino-purulent exudate on the pulmonary pleura is often found, but larger amounts of free exudate are less common. Any free exudate is usually a thin, turbid, slightly blood-stained fluid. Creamy pus is rarely met with in the early neonatal period. Pleural infections are in newborn infants, as at a later age, almost invariably secondary to a pulmonary involvement. There is, however, evidence of an occasional haematogenous infection of the pleura with secondary involvement of the subpleural lymph-vessels and lung parenchyma (Macgregor, 1939).

The tissues of the neck are now extensively exposed by passing the knife in a lateral direction between the skin and the deeper structures. The sternocleidomastoid muscle is thoroughly examined for the presence of injury. If fibrous tissue is seen within the muscle, a piece is taken and histologically examined for haemosiderin. If a swelling of the parotid was noticed on external examination the gland can be approached from the incision in the neck and slices can be taken for histological and bacteriological examination. A purulent parotitis is not uncommonly the first, or even the only, manifestation of a septic infection in the newborn. It may perforate into the external auditory meatus.

A pointed knife is now passed upwards in the midline between the tongue and the mandible, close to the latter. The incision is extended laterally and backwards along the arch of the mandible and close to the latter down to within a few millimetres of the angle. After this procedure has been carried out on both sides the tongue is pulled forwards and downwards beneath the mandible with the aid of forceps. A pointed knife is inserted in the midline between the hard and soft palate, an arched incision is made between these two structures and extended sidewards and downwards into the wall of the pharynx and the soft tissues of the neck, always keeping as far laterally as possible.

This incision being completed on both sides, the knife is placed between the posterior wall of the pharynx and the spine, the pharynx and the upper part of the oesophagus are separated from the latter and pulled downwards and forwards, leaving the main muscles of the neck and the large blood-vessels in the body. Each lung in succession is extroverted anteriorly and medially, the dome of the pleura is incised, and the blood-vessels of the neck are severed as high as possible. The tongue, with the pharynx and larynx, are now firmly seized by the right hand and pulled vigorously downwards, thus separating all thoracic organs down to the diaphragm. Only exceptionally are there such pleural adhesions that separation with the help of a knife is necessary.

The spleen is shifted by the left hand away from the ribs, and the diaphragm is incised along its insertion. A similar procedure is carried out on the right side between the liver and the ribs. All abdominal organs together are separated from the posterior abdominal wall, and the dissection is continued along the wall of the pelvis. Finally, the symphysis is severed with a cartilage knife, the urethra or vagina is severed and the incision is extended backwards and the organs are finally freed and taken out of the body. If, however, inspection revealed evidence of malformation of the urinary tract, the necessary dissection is in the male somewhat laborious, in order to avoid external mutilation. The prostatic part of the urethra is exposed, held with a forceps, traction is exerted, and the urethra with corpus spongiosum, corpora cavernosa and glans penis are removed by careful dissection, leaving the skin intact. The skin can subsequently be packed with cotton wool.

The seventh rib is cut with a cartilage knife longitudinally and perpendicularly to its surface, a slice of about 1-2 mm. in thickness is removed, and the costochondral junction is inspected for the presence of osteochondritis syphilitica. The latter is suggested by a broadening and irregularity of the provisional calcification zone, which is also more yellow and brittle than normal. Softening, greyish discoloration, grey or yellow areas of soft tissue in the subepiphyseal zone, due to proliferation of syphilitic granulation tissue, may be found in more advanced cases. One should never be satisfied with a negative finding in the ribs, but the lower end of the femur should also be examined. Syphilitic osteochondritis of the newborn may be associated with juxta-epiphyseal periostitis and epiphyseal separation may also be found, but confusion with artifacts from sawing has to be avoided. To avoid this confusion L. Pick (1929) recommends the use of an electric "band saw" after freezing of the bone. In the early neonatal period syphilitic osteochondritis is always associated with visceral syphilis. Rickets is not found before the third month of life in full-term infants, or before the end of the second month in immature babies. Congenital rickets has, however, been described by Maxwell, Hu & Turnbull (1932) in Chinese babies of osteomalacic mothers. Early rickets can be recognized on histological examination only, and partial decalcification with Müller's fluid is very useful for the demonstration of osteoid borders.

IV. EXAMINATION OF VISCERA

The examination of the organs removed "en masse" is now undertaken. The soft palate is cut through in the midline, the pharynx, the epiglottis and the tonsils are inspected, and incisions are made into the latter. Although rare, purulent tonsillitis may be found in the neonatal period. All organs are placed on a board in such a way that the pathologist faces their posterior aspect. The aorta is severed above the diaphragm and its posterior wall is incised longitudinally, extending the incision into the left subclavian artery. Any blood is removed, the aorta is washed with running water and inspected. Attention is to be paid to any icteric discoloration of the intima, to the orifice of the ductus arteriosus, and to the presence or absence of a coarctation of the aorta, which is usually situated in the level just above or just below this orifice (isthmus stenosis).

Although circulation in the ductus arteriosus ceases almost immediately after birth (Barclay, Barcroft, Barron & Franklin, 1938 ; 1939), the anatomical obliteration is a slow process usually commencing at the pulmonary end, and in the majority of cases it is not completed until the end of the second

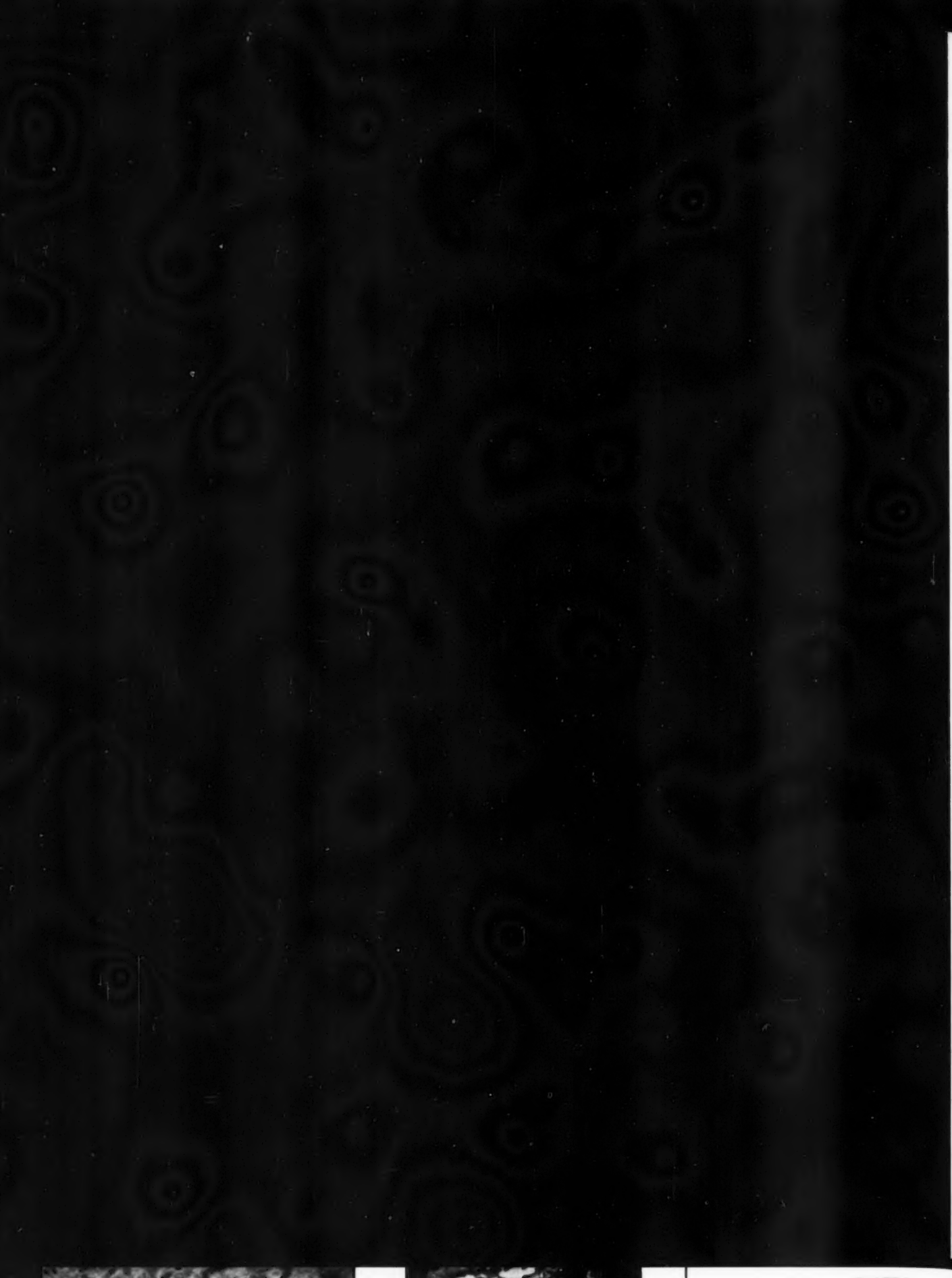


PLATE I

POST-MORTEM APPEARANCES IN THE NEWBORN

(FIGS. 2-14)

H. S. Baar

FIG. 2

FIG. 2. Macerated fœtus with hydrops fœtalis.

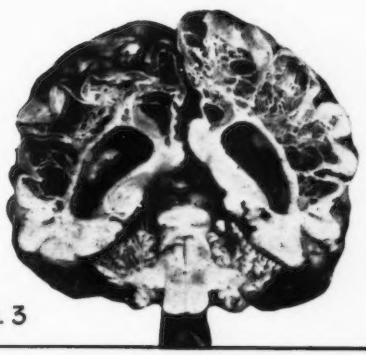


FIG. 3

FIG. 3. Encephaloclastic porencephaly.

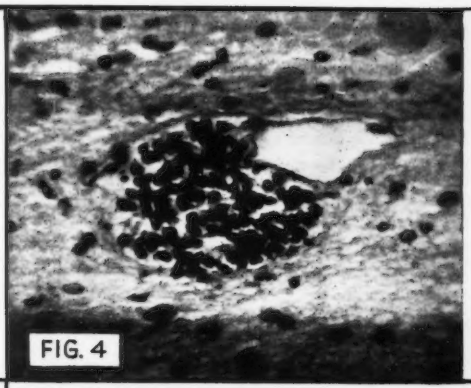


FIG. 4

FIG. 4. Perivascular crescent in Virchow's "Encephalitis interstitialis neonatorum."

FIG. 5

FIG. 5. Coarse subependymal granulations in a case of infective encephalitis of the newborn resembling toxoplasmosis.

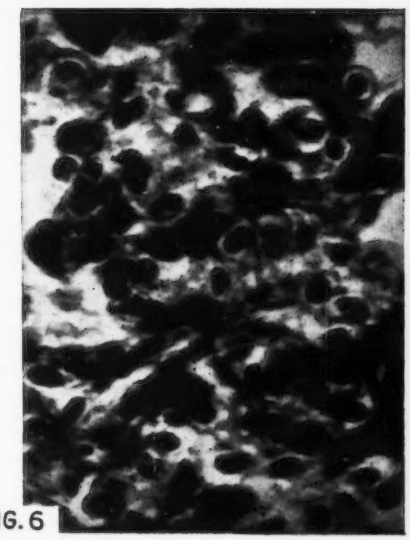


FIG. 6

FIG. 6. Initial atelectasis of the newborn.

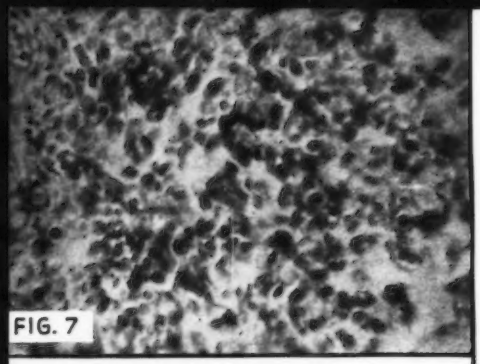


FIG. 7

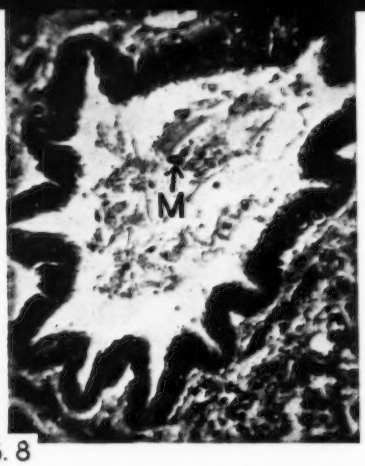


FIG. 8

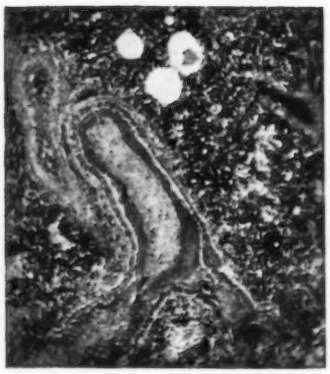


FIG. 9

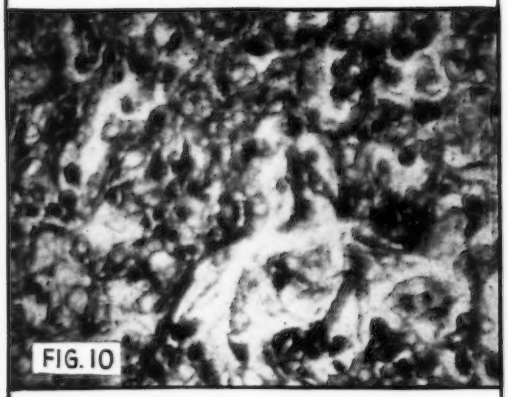


FIG. 10

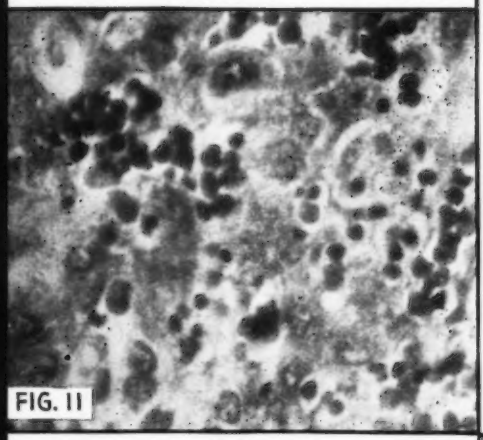


FIG. 11

FIG. 12

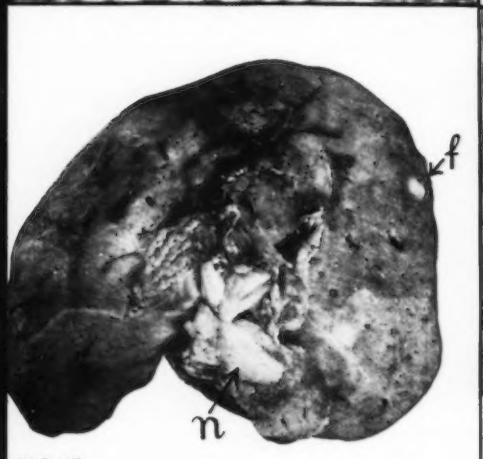


FIG. 13

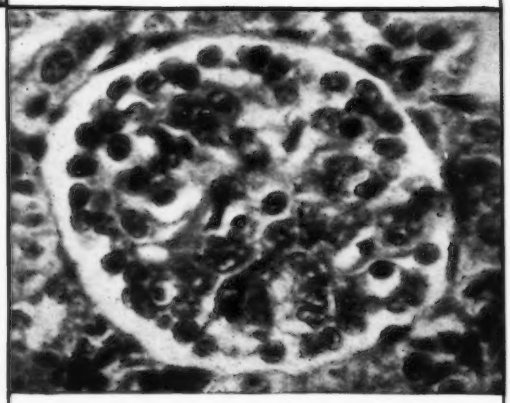


FIG. 14

FIG. 7. "Resorptive atelectasis" of the newborn.

FIG. 8. Squamous cornified epithelial cells and meconium-body (M) in a bronchus of a stillborn infant.

FIG. 9. "Vernix membrane" in a small bronchus of a newborn infant.

FIG. 10. Squamous epithelial cells and vernix membranes in an alveolar duct of a newborn infant.

FIG. 11. Haematopoiesis in the liver of an immature infant (seven months gestation). The baby died 15 minutes after birth. The cause of death was an intrapericardial teratoid neoplasm.

FIG. 12. Non-syphilitic miliary necroses of the liver in a six weeks old infant.

FIG. 13. Primary tuberculous complex of the liver in a case of congenital transplacental tuberculosis.
f = primary focus.
n = caseated lymphnodes ad portam hepatis.

FIG. 14. Bloodless partly-hyalinized glomerulus in kidney of newborn infant.

month of life. A partial anatomical obliteration is often present at the age of 3-4 weeks, and the central part may remain open for a long time after the pulmonary and aortic ends are obliterated (Jager & Wollenman, 1942). Mönckeberg (1924) accepts a patent ductus arteriosus as pathological only if it is found after the age of three months. Probing of the duct should be postponed until the heart has been dissected, and is carried out from the pulmonary orifice which is seen just above the division into the right and left branches.

The proximal part of the aorta should be inspected for an anomalous right subclavian artery (arising from the descending aorta and turning upwards and to the right side behind or before the oesophagus—" dysphagia lusoria ") and for an aberrant ductus arteriosus (very rare). The aorta is separated from the oesophagus and turned over the left main bronchus in front of the left lung. The oesophagus is inspected. A saccular dilatation of its upper part indicates the presence of an atresia ; in the common form the upper part forms a wide blind sac, while the lower part is normal in width and communicates with the trachea just above the bifurcation by a narrow fistula. In such a case each part separately is cut longitudinally and a probe is passed from the opening at the proximal end of the lower part into the trachea and larynx to demonstrate the presence of a fistula. Other forms of oesophageal atresia are very rare. If nothing abnormal is seen on external examination of the oesophagus, it is slit along its posterior wall from the pharynx downwards.

White patches the size of a pin's head or, by their confluence, white membranes of thrush, which are firmly adherent to the oesophageal wall, are very common in newborn infants. The writer does not agree with the view, which has gained ground in recent years, that the thrush produces inflammatory changes, but he believes that it is a saprophyte growing readily on tissues either damaged mechanically or chemically (HCl of gastric juice) or reduced in their vitality by marasmus.

The oesophagus is carefully separated from the trachea, after having been severed above the diaphragm, with the help of scissors, leaving the paratracheal lymph-nodes and parathyroids *in situ*. The lower parathyroids are exposed by following the inferior thyroid artery, the upper by careful dissection of the tissues between the oesophagus and the thyroid. There is much variation in the number and the situation of the parathyroids, and they may be embedded in the thyroid or, in the case of the upper ones, in the thymus. Microscopical haemorrhages and later pigmentation are very frequent in infantile parathyroids. In the postneonatal period, pigmentation is found as frequently in normal infants as in those with tetany, and there is no relationship between parathyroid haemorrhage of the newborn and tetany of later infancy. The rare tetany of the newborn, however, may be occasionally caused by massive haemorrhagic destruction of parathyroids (Tezner, 1927 ; Baar, 1937). The thyroid is inspected and incised. Severe congestion of the thyroid is common in asphyxia of the newborn. Congenital goitre is common in such countries as Styria, and may be occasionally the cause of suffocation. Complete absence of the thyroid (thyreoaplasia) is the common cause of " congenital myxoedema."

Respiratory Organs and Thymus

After examination of the tracheo-bronchial lymph-nodes, the trachea is slit along its posterior wall and the incision is extended into the main bronchi. Large amounts of fluid, mucus, or muco-purulent exudate, may be found in the trachea, which should be examined microscopically for elements of liquor amnii. The problem of aspiration of amniotic fluid as evidence of intra-uterine asphyxia has been elucidated by the work of Johnson & Meyer (1925), Farber & Sweet (1931), and Macgregor (1939). As early as the sixteenth century, Vesalius observed that disturbance of the placental circulation in an animal foetus brought about definite respiratory movements resulting in aspiration of liquor amnii. This problem, about which there was much controversy, has been clarified by the admirable work of Barcroft (1942). Some intra-uterine respiratory movements appear to be physiological (Patterson & Farr, 1939), but the writer agrees with Macgregor that large amounts of aspirated liquor amnii are always evidence of intra-uterine asphyxia. The resulting inflammatory changes in the bronchial tree and in the pulmonary parenchyma may be abacterial, due to irritative action of vernix caseosa, and thus comparable with the " physiological " foreign-body otitis media of the newborn. Large amounts of amniotic fluid may prevent expansion of the lungs, and accumulation of mucus as a result of irritation may produce a secondary obstruction.

The inspection of the pleurae frequently reveals pin-head-sized, sometimes hempseed- to lentil-sized [2-4 mm.], subpleural haemorrhages. In the examination of the lungs, which are incised by any of the routine methods, there are great difficulties in the differentiation of atelectasis, pneumonia and massive haemorrhage, and a final opinion should be given only after histological examination. Atelectatic lungs are purplish-red in colour and fleshy in consistency, contrasting with the pale pink aerated areas which are mainly localized in the anterior parts of upper lobes. In the presence of aerated areas in the lungs of still-born infants, the possibility of artificial respiration has always to be taken into account. Diffuse pneumonic changes can easily be confused with collapsed parenchyma, but patchy pneumonic areas are often felt as areas of firmer consistency even in collapsed lungs, and may be seen to project slightly on the cut surface. Massive haemorrhage and haemorrhagic pneumonia are very similar on palpation and macroscopic examination. The former, however, is usually more extensive, but it should be remembered that pneumonic changes occur often secondarily in areas of massive haemorrhage. Histological examination will usually enable the distinction to be made. Interstitial emphysema, sometimes very marked in newborn infants, is always evidence of inflammatory changes or of obstruction, being the result of alveolar rupture. Histological examination of the lungs of newborn infants reveals a surprising frequency of inflammatory changes. Microscopical examination is also necessary to differentiate " initial " from " resorptive " atelectasis, and for the demonstration of anatomical immaturity of lungs (Farber & Wilson, 1933 ; Wilson & Farber, 1933). Lungs with initial atelectasis show a " glandular " appearance, with tubules of cubical epithelium lining a slit-like lumen, in contradistinction to resorptive atelectasis, where the lining is a flattened epithelium. If the initial atelectasis is incomplete (partial aeration) the lumen is wider and more saccular in shape, but the lining is still cubical. Atelectasis, especially resorptive, is always associated with engorgement of the capillaries of interalveolar septa (Fig. 6, 7). In the lungs of immature infants clusters or masses of cells resembling alveolar epithelia are seen without a trace of a lumen (unexpandable areas, Farber & Wilson, 1933).

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Pneumonia of the newborn may be due to aspiration of amniotic fluid, aspiration of vomited material, aerogenous and haematogenous infection. The first type is the most interesting. Cornified squamous epithelial cells are found in the bronchi, bronchioli and air sacs. They appear as wavy lines or as cells, dome-shaped in the centre and tapering towards both sides. Nuclei are usually absent. Lanugo hairs may also be seen, and occasionally particles of meconium recognizable as a yellowish amorphous mass or as greenish-yellow spherical or ovoid bodies—Huber's meconium bodies. A characteristic feature, though not always present, is the " hyaline membrane " (Johnson & Meyer, 1925) or " vernix membrane " (Farber & Sweet, 1931). This is a homogenous membrane, pink or bright red in haematoxylin-eosin stained sections, lining the bronchioli and alveoli. It resembles the hyaline membrane in influenza (Wolbach, 1919), but squamous epithelial cells may be seen within the membrane, and Sudan stain reveals the presence of fatty material while fibrin is absent. It results from elements of the vernix caseosa being flattened by the entering air or fluid against the walls. Such findings may be met with in the absence of pneumonia, or inflammatory cells may be present in the alveoli (Fig. 8, 9, 10).

Haemorrhagic pneumonia is very frequent in the neonatal period. It often results from aspiration, postnatal more frequently than intra-uterine. If the necropsy is made some time after death, pneumonic areas from aspiration of vomited material may assume a brownish colour due to the formation of acid haematin from haemoglobin. Such areas are not to be confused with the soft " digested " brown areas due to post-mortem changes in uninflamed areas after terminal aspiration of gastric contents.

Aerogenous pneumonia is associated with exudative bronchitis and cellular alveolar exudate. Mural bronchitis and peribronchitis are moderate or absent. The main localization of aerogenous pneumonia in newborn infants, as in later infancy, is in the postero-inferior part of the right upper lobe, the part of the lung which has physiologically the poorest aeration. In marasmic infants of the later neonatal period, paravertebral pneumonia is often found. This forms thin subpleural strips of consolidated parenchyma in the posterior paravertebral parts of both lungs. It extends usually only a few millimetres beneath the pleura, and the differentiation from collapse in these areas is often difficult.

Septic haematogenous infection of the lungs results in septic haemorrhagic infarcts, in an infarct pneumonia, sometimes in multiple, small, symmetrical abscesses. The septic haemorrhagic infarcts may resemble aseptic infarcts, but there is usually a narrow yellowish demarcation zone. Empyema of the pleural cavity or fibrino-purulent pleurisy is always present in pyaemic infections of the lungs. Purulent pleurisy of the left side is often associated with fibrino-purulent or fibrinous perisplenitis. Pneumonia of the newborn is sometimes caused by *B. coli*. This type of infection occurs only in the neonatal period (Macgregor, 1939), but care is needed in the interpretation of bacteriological post-mortem findings, because of the possibility of post-mortem invasion of the blood-stream and the tissues from the intestine. Direct smears and their correlation with cultural findings are indispensable.

Tuberculous infection of the lungs is only exceptionally met with in the neonatal period, but congenital transplacental tuberculosis with a typical primary complex in the liver (Fig. 13) may be associated with a simultaneous infection of lungs via the ductus venosus, and results in the formation of a (usually progressive and cavitating) pulmonary complex in addition to that in the liver.

A primary inhalation tuberculosis is only exceptionally discovered in the post-mortem examination of newborn infants in the absence of caseation. The early primary focus may resemble an unspecific consolidation, although usually it is more sharply demarcated. Histological examination reveals a mononuclear infiltration of the interalveolar septa and mononuclear exudate in the alveoli with acid- and alcohol-fast bacilli (Pagel & Price, 1943). Exceptionally the exudate is polymorphonuclear or shows microscopical caseation (Zarfl, 1912 ; Beitzke, 1930). Such lesions are likely to remain unrecognized unless attention has been drawn to such a possibility by the clinical history.

Syphilitic pneumonia alba is extremely rare in live-born infants, but not uncommon in syphilitic still-births.

The anterior mediastinum and the thymus are inspected and the latter is incised for the presence of " Dubois abscesses ". Hyperplasia of the thymus is more often diagnosed than really present. Weights up to 20 and probably 25 g. should be considered as normal in the neonatal period. A definite hyperplasia of the thymus, associated with general hyperplasia of the lymphadenoid tissue, is evidence of an abnormal constitution, but is never the cause of death, and the existence of a thymic stridor or thymic asthma is not supported by post-mortem examinations.

Heart, Pericardium, and Vessels

The pericardial sac is opened and the pericardium, epicardium, heart, aorta and pulmonary artery are thoroughly inspected. Subepicardial haemorrhages, " taches du Tardieu," are not pathognomonic of asphyxia, since punctate subepicardial haemorrhages also occur in septic conditions and in haemolytic and haemorrhagic disease of the newborn. Streak-like subepicardial and myocardial haemorrhages are, however, very suggestive of asphyxia. Fibrino-purulent pericarditis associated with mediastinitis is occasionally seen in the later neonatal period as a sequel of purulent pleurisy. The size of the heart in a newborn infant, as later, is approximately that of its clenched fist.

The necessity for special technique in the examination of each organ applies particularly to the heart. Especially in the various forms of transposition of great vessels, the most suitable technique has to be considered thoroughly before starting with the dissection. The discussion of the pathology of congenital heart disease is beyond the scope of the present paper, and the monograph and atlas of Abbott (1927, 1936), the monograph of Mönckeberg (1924), and the papers of Spitzer (1923) and of Harris & Farber (1939) should be consulted for this purpose.

If there appears to be no necessity for a special technique, Rokitansky's method, slightly modified, has proved most satisfactory. In this method the heart is grasped with the left hand around its right border, an incision is made with a pointed knife into the lower end of the left border of the left ventricle, the ventricle is opened and all clots are removed. The knife is then passed through the mitral orifice to the point where the left pulmonary veins join the left auricle, and the incision is extended, thus exposing the left ventricle and auricle. Further clots are removed, the chambers are washed with running water, and gently dried with a sponge.

The chambers and the mitral valve can now be inspected. Tiny blackish nodules in the mitral valve, the so-called valvular haematomata or valvular angiomata, are not uncommon in the neonatal period. They are remnants of the embryonic vascularization of the valve, and are without pathological significance. The heart is now grasped with the left hand around the left ventricle, and an incision is made into the right border of the right ventricle. With the help of long scissors this incision is extended into the superior vena cava.

After having been cleaned, the chambers of the right side and the tricuspid valve can be inspected. Thin threads in the right auricle, " the network of Chiari," are a developmental abnormality without pathological significance. The foramen ovale shows in the majority of cases a valvular patency only. A crescentic patency in the antero-inferior part 1-2 mm. in width is, however, within the limits of normal. In determining whether the patency is pathological or not, the presence of an enlargement of the heart is more important than the size of the opening.

The heart is now placed in such a way that the pathologist faces the pulmonary artery. Scissors are passed into the artery and an incision is made along its left (really anterior) margin. The pulmonary conus, valve and artery are inspected, and if necessary a probe is passed into the ductus arteriosus. The aorta is next examined by passing the scissors behind the anterior cusp of the mitral valve, so that in opening the aorta the pulmonary artery is cut just above its valve. The three cusps of the aortic valve are now seen—the anterior in the middle, the right and left with their coronary ostia on each side. A bicuspid aortic valve is not a very uncommon finding. Such a valve has to be examined histologically to decide whether the condition is developmental or inflammatory. Special attention is to be paid to the pars membranacea of the interventricular septum, where patency is comparatively frequent. Large or small openings may be found in any part of the interventricular septum, those at the lower end being often small and easily overlooked. It would be erroneous to consider every heart disease in a newborn infant as a developmental error, because foetal endocarditis, although rare, certainly does occur. A marked hypertrophy without developmental errors or foetal endocarditis is very suggestive of cardiomegalia glycogenica, which may occur without glycogen storage in the liver. In such case, a piece of tissue is taken for quantitative glycogen estimation and another to be fixed in Lison's (1936) modification of Bouin's fluid (8·5 cm.³ dioxane saturated with picric acid ; 1 cm.³ concentrated formaldehyde solution ; 0·5 cm.³ glacial acetic acid) for Best's carmine stain. Sometimes a hypertrophy of the heart of obscure origin is encountered in the neonatal period, the so-called idiopathic hypertrophy of the heart in the newborn, and rarely an enlargement of the heart is due to a rhabdomyoma.

Stomach, Liver and Bile-ducts, Spleen

The examination of the abdominal organs is started with the opening of the stomach by an incision in the anterior wall parallel to the greater curvature ; the incision is extended into the duodenum. Peptic gastric or duodenal ulcers occur in the early neonatal period and in marasmic babies in later infancy, and may be the cause of melaena neonatorum. The pylorus in congenital hypertrophic pyloric stenosis is hard, feels like cartilage, and shows a marked thickening of the wall, the hypertrophic muscular coat being conspicuous by its greyish-white colour. The normal thickness of the pyloric wall is 1·5-2 mm. In pyloric stenosis it is usually 3·5-7 mm. The figure 3·5 mm. as the upper limit of the normal given by some authors is, in the writer's experience, too high. A hypertrophy of the body of the stomach was seen by the writer in three cases of pyloric stenosis.

The patency of bile-ducts is examined by manual pressure on the gall-bladder and by probing common bile-duct from the papilla of Vater. A probe can also be passed into the pancreatic duct, but this procedure is not advisable because, in normal infants, a thin probe can be passed only for a short distance, and the duct is damaged, thus making the interpretation of histological findings difficult. If fibrocystic disease of the pancreas is suspected, conclusive information about the condition of the ducts can be obtained only from serial sections. In this disease, the pancreas may be harder than normal. The normal pancreas of young infants is much softer than that of older children. Only exceptionally an abnormal structure may be noticed on section in naked-eye examination, and in the majority of cases fibrocystic disease of the pancreas is discovered only on histological examination. It should be suspected in all cases of meconium ileus (*vide infra*), or obliteration of the small intestine. Among 38 cases of cystic fibrosis of the pancreas studied at the Children's Hospital, Birmingham, there were 7 cases in the early neonatal period, 4 being associated with meconium ileus, one with suprapapillary and one with intrapapillary duodenal atresia, and one with atresia of the lower ileum. The association with bronchiectases, suppurating pneumonia and peribronchial abscesses, which is common in later infancy, does not occur in the early neonatal period.

Only a few of the numerous pathological conditions of the liver seen in newborn infants can be mentioned. In congenital obliteration of bile-ducts, the liver is enlarged, dark green and hard, its surface being either smooth or finely granular. The cut surface shows green dots separated by strands and spots of grey tissue, the strands forming a network in many places, and a similar appearance may be found without obliteration of extrahepatic bile-ducts (Parsons & Hickmans, 1926). Infective biliary cirrhosis (Rössle's cholangitic biliary cirrhosis) is not rare in the neonatal period. On histological examination it usually does not present the features of a pure " perilobular " cirrhosis, but shows a marked ingrowth of fibrous tissue into the individual lobuli. In infants surviving for a longer period, a distortion of the hepatic structure may be found comparable only with that seen in syphilitic hepatitis. Biliary cirrhosis may also be found as a sequel of icterus gravis neonatorum in infants surviving for some weeks. In infants with icterus gravis dying in the first days of life, the liver is either green or reddish brown, moderately firm, and on section the lobular structure is indistinct or not discernible, Perl's reaction is strongly positive. On histological examination in all cases of haemolytic disease of the newborn, the liver shows, all over the section, dilated capillaries packed with nucleated erythrocytes. In livers of normal full-term babies, only an occasional haematopoietic focus is seen, but the liver of an immature infant dying in the early neonatal period may be indistinguishable from that in haemolytic disease, except for the marked haemosiderosis in the latter condition (Fig. 11). Dilated bile-capillaries, bile-thrombi and small areas of

necrosis or necrobiosis are not uncommonly seen in icterus gravis.

The liver in Pepper's type of congenital sympathicoblastoma has a very characteristic appearance. It is enormously enlarged and studded with lentil- to pea-sized [2-4 mm.] greyish-white or yellowish nodules, some of which show haemorrhagic areas.

The liver in congenital syphilis is enlarged, firm, reddish-brown or greyish-red, only exceptionally greenish. On section, all traces of lobular structure have disappeared and are replaced by irregular spots and strands of reddish-brown, grey and pinkish-grey tissue. An association of this diffuse syphilitic hepatitis with miliary granulomata is not uncommon, but the latter (erroneously called miliary gummata) are never seen without diffuse hepatitis. The characteristic histological findings need not be discussed here. Smears for Fontana's stain should be always made in addition to Levaditi's stain in sections. Miliary non-syphilitic necroses of the liver are rare, but occur almost exclusively in young infants, the liver being studded with millet-sized [1·5-2 mm.] yellowish nodules which are visible both on surface and on section, where they often show a central depression (Fig. 12). Their pathogenesis is obscure, although they are usually associated with severe enteritis or with umbilical sepsis. Similar necroses were described in infantile toxoplasmosis, and were seen by Parsons & Baar (1945) in one of their cases of infective encephalitis resembling toxoplasmosis.

A typical primary tuberculous complex of the liver in congenital transplacental tuberculosis is shown in Fig. 13.

Glycogen-storage disease (van Creveld-Gierke's disease) should be suspected when a very large liver without characteristic naked-eye appearance is found in the absence of a splenic tumour. Apart from investigations for glycogen, the speed of glycogenolysis should be determined. Blood-sugar estimations are of value only if the necropsy is made shortly after death, and only blood from the left side of the heart should be used, never that from the right.

Marked fatty changes in the liver may be found as early as 24 hours after birth.

The ligamentum hepato-duodenale is now inspected, and the portal vein is opened for the presence of thrombosis.

The spleen is enlarged in septic conditions of the newborn, but a typical acute splenic tumour with diffluent pulp is never seen. Large hard splenic tumours are seen in syphilis, in congenital tuberculosis, in biliary cirrhosis, in haemolytic disease of the newborn, in congenital leukaemia and, particularly large, in Niemann-Pick's disease and the infantile form of Gaucher's disease . In sphyngomyelin lipoidosis (Niemann-Pick's disease), the liver is also considerably enlarged, and the enormous spleen shows on its cut surface a peculiar salmon-pink colour, sometimes with areas of more greyish-pink colour. Tissue should be taken for paraffin sections, for frozen sections and for lipid analysis (which alone enables a definite diagnosis to be made).

Hodgkin's disease is extremely rare in the neonatal period, but a case of congenital Hodgkin's disease as the result of transplacental transmission has been described by Priesel & Winkelbauer (1926). The spleen is the only organ with an absolutely characteristic naked-eye appearance. It has the features of a " porphyry spleen."

The abdominal aorta and inferior vena cava are dissected and examined. Thrombosis of the abdominal aorta in the neonatal period associated with anaemic infarction of the liver has been described by Morrison (1945). Thrombi in the inferior vena cava are not rare.

Suprarenal Glands

The pathology of the suprarenal glands is of great importance in the neonatal period. Haemorrhages of the suprarenal are not uncommon as the result of birth-injury, but the writer has never seen the Waterhouse-Friderichsen syndrome resulting from septic infections in the neonatal period. Haemorrhages of the suprarenals should not be confused with the physiological hyperaemia (sometimes erroneously called physiological haemorrhage) of the inner zone of the cortex and its post-mortem softening. Small haemorrhages are often found on histological examination. Even large haemorrhages may be compatible with life, and on two occasions the writer has observed, as an incidental finding in older children, extensive destruction, calcification and deposition of haemosiderin in both adrenals, leaving only about one-fourth to one-third of suprarenal tissue intact. Suprarenal haemorrhage of the newborn is almost invariably associated with intracranial haemorrhages, and is supposed to be the result of asphyxial congestion.

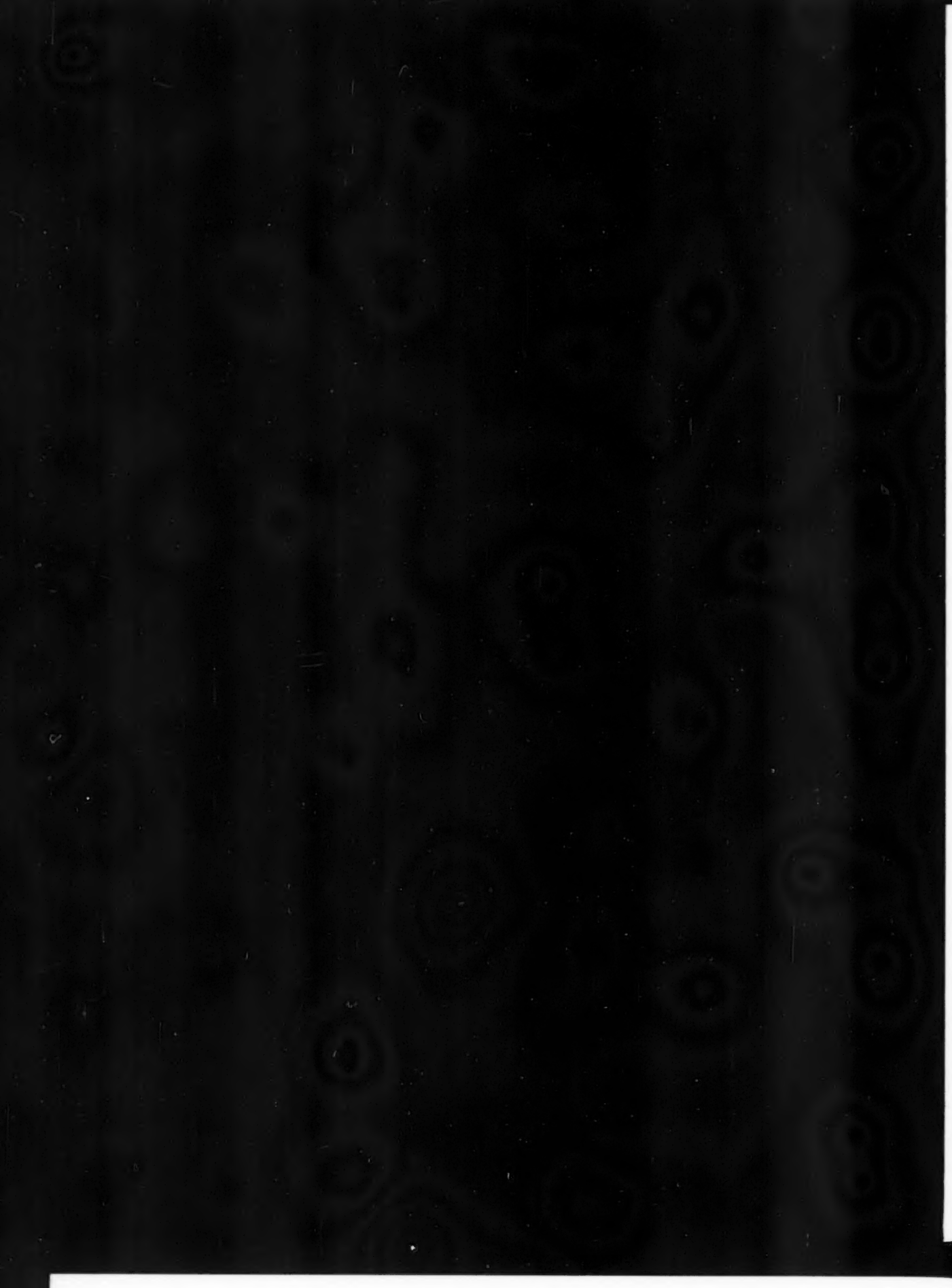
Hyperplasia of the suprarenals is in the newborn female always associated with pseudohermaphroditism. The external genitalia are of the male type, the internal—except for occasional ovotestes (Broster, Clifford, Vines, Patterson, Greenwood, Marrian & Butler, 1938)—normal female. In the rare cases of suprarenal hyperplasia with male gonads there is no pseudo-hermaphroditism. The prostate is enlarged, the testes are normal. Although in later childhood interrenal pseudo-hermaphroditism is always associated with precocious growth and ossification, the writer has failed to find any increase in length or premature ossification centres in newborn pseudo-hermaphrodites with suprarenal hyperplasia. Adrenal hyperplasia in young babies dying with symptoms of gastro-intestinal stenosis has been described by Dijkhuizen & Behr (1940). Two cases of this type were seen at the Children's Hospital, Birmingham, both having been sent to the hospital with the diagnosis of pyloric stenosis.

In normal newborn infants, the suprarenal is about one-third of the kidney's size. In hyperplasia it is not only considerably enlarged but also more firm, and its surface shows numerous deep furrows. Sections of suprarenals should be stained in such cases by the method of Vines (1938), although it is still debatable whether the fuchsinophil granules are the site of androgenic hormone.

Sympathicoblastoma of the suprarenal in the newborn infant has already been briefly discussed. A case of apparently primarily multiple neuroblastomata (=sympathicoblastoma), ganglioneuromata and neurofibromata in a still-born infant has been described by Potter & Parish (1942).

Urinary Organs

The kidneys of the newborn infant show marked foetal lobulation, and in infants more than two days old the so-called " uric acid infarcts " (Virchow) are often seen as golden-yellow radiating streaks in the renal pyramids. The mechanism of their formation is still obscure, but dehydration certainly plays an important role (Czerny & Keller, 1925). In the late neonatal period and in later infancy, dehydration is associated with urate concretions in the renal pelves, instead of uric acid infarcts. Renal calcinosis, which may be



occasionally seen in the later neonatal period, is in its milder degrees only microscopically recognizable. In more advanced cases dry, white, chalky streaks and spots are seen on naked-eye examination; these are due to lime casts and calcium deposition in necrotic epithelia. They are usually associated with severe diarrhoea and are, in the writer's opinion, secondary to the loss of bases necessitating the use of calcium for neutralization purposes. Severe renal calcinosis may be the cause of uraemia. Extreme hypoplasia of both kidneys is another cause of uraemia in the neonatal period. The size of such a kidney may be that of a bean [12-14×4-5 mm.]. Focal scarring of kidneys with depressions resembling arteriosclerotic depressions has been seen on one occasion as a result of intra-partum haemorrhage. Haemorrhagic infarction of kidneys, total or partial, is not uncommon in the neonatal period, and is the result of thrombosis of renal vein. If the main vein is involved, the thrombus may extend into the inferior vena cava, or a thrombus may be seen projecting out of the renal vein into the latter. Congenital hydronephrosis and hydroureter are only in a minority of cases due to an organic obstruction, and the majority have not yet been satisfactorily explained, although partial gigantism or achalasia of sphincters have been suggested. The latter explanation is more probable, especially in cases with marked hypertrophy of the wall of the urinary bladder. Secondary infection resulting in pyonephrosis may be seen in the neonatal period.

Endothelial proliferation and hyalinization in arterioles and glomeruli (Fig. 14), proliferation in the parietal layer of Bowman's capsule and fusion with the tuft are frequently found in kidneys of newborn infants ("congenital glomerulosclerosis") (Herxheimer, 1909; Friedman, Grayzel & Lederer, 1942). They are focal in distribution, usually very scanty, disappear in early childhood, and are probably in the majority of cases without pathological significance (? developmental in origin). It is difficult to correlate these findings with the physiological albuminuria of the newborn, and more likely that the latter is due to the changes in the epithelium of the visceral layer of Bowman's capsule, described by Gruenwald & Popper (1940).

A Wilms' tumour may be congenital. The youngest baby from which a specimen of Wilms' nephroblastoma has been examined by the writer was 6 weeks old.

Haemorrhagic glomerulonephritis has been seen on a few occasions in newborn babies of mothers suffering from eclampsia gravidarum.

Haemorrhagic or gangrenous cystitis is often seen in infants with rectovesical fistula, and is usually associated with unilateral or bilateral pyelonephritis. A urachus cyst interfering with the contractions of the bladder was apparently the cause of urinary stagnation, infection, and pyelonephritis in one case observed at the Children's Hospital, Birmingham.

Gross malformation of the genitalia is occasionally associated with malformation of the urinary tract. Follicular cysts of the ovary are comparatively often found.

Intestine

The intestine is dissected with scissors from the rectum upwards to the caecum, the scissors are passed through the ileo-caecal valve, and the small intestine is dissected along its mesenteric insertion. The contents of the intestine are thoroughly inspected. Those of the large intestine give often the only evidence of the presence of an "enteritis". An interesting condition of the early neonatal period is the meconium ileus, which is almost invariably associated with cystic fibrosis of the pancreas. It was first described by Landsteiner (1905). The large intestine is collapsed and almost empty, and a plug of pale inspissated meconium is found blocking the ileo-caecal valve. Similar material, which has been well compared with putty, is found in the small intestine. Occasionally, however, only the lower part of the small intestine contains this material, while green soft meconium may be found in the upper part. These babies die of a diffuse peritonitis.

Blood or blood-stained meconium may be found in the intestine in haemorrhagic disease of the newborn. Ulcers, mainly duodenal, are found only in a few children who have suffered from intestinal bleeding. The haemorrhage is usually parenchymatous and is often associated with submucous haemorrhages. Some authors, however, have reported the frequent finding of tiny ulcers on microscopical examination.

Diarrhoea of the early neonatal period is more often associated with anatomical changes in the intestine than is the case in later infancy. It may be haemorrhagic or ulcerative. "Transmigration" or "permeation" peritonitis is not uncommonly associated with this type of enteritis, and may occur even in an enteritis without gross anatomical changes of the intestinal wall. It is interesting evidence of the immaturity of the neonatal intestine. Haemorrhagic and ulcerative enteritis of the later neonatal period is sometimes associated with intestinal pneumatosis (intestinal emphysema). In this condition, innumerable tiny air-vesicles are seen in the intestinal wall, which on palpation gives a feeling similar to that of an aerated lung. Previously considered as a post-mortem phenomenon, it is now recognized by the majority of authors as an intravital change. On histological examination, the vesicles are usually found in the corium mucosae and in the submucosa. Bacteria are not seen in the surrounding tissue, and in the majority of cases there are no inflammatory changes. The condition is probably due to a mechanical pushing of air through the damaged mucosa by intestinal peristalsis.

In the majority of cases with fatal diarrhoea, in the neonatal period as well as in later infancy, the anatomical and bacteriological findings are negative, except for the frequent fatty degeneration of the liver, and, in spite of the enormous amount of work which has been done to elucidate this most important problem, the pathologist remains puzzled and dissatisfied.

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A SUMMARY OF PRESENT KNOWLEDGE OF HUMAN BLOOD-GROUPS, WITH SPECIAL REFERENCE TO SEROLOGICAL INCOMPATIBILITY AS A CAUSE OF CONGENITAL DISEASE

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Inheritance of the Blood-Groups

Since Landsteiner's discovery of the ABO blood-groups at the beginning of this century a great deal has been learnt about the inheritance of blood-group antigens, but almost nothing about the inheritance of blood-group antibodies. It is still a matter of conjecture why a person who possesses antigen A has anti-B in his serum. The reciprocal arrangement of antigens and antibodies is found as a rule only in the ABO groups, but is not complete in this system, for AB persons very rarely have anti-O in their serum, and the subgroup antibodies are not regular in their appearance. For example, it is only one in three A_2B persons who has α_1 (anti-A_1) in his serum. This is in such a sharp contrast with the regularity of the appearance of the antigens as to suggest that either the presence of antibodies is not wholly genetically determined, or, if it is, that the mechanism of inheritance is of a more complicated nature than that controlling the antigens.

The antibodies corresponding to the other blood-group antigens seldom occur naturally. For example, a person of group N very rarely has anti-M in his serum. Even more rarely has an M person anti-N. Anti-P is only occasionally found in blood lacking that antigen, and as far as I am aware anti-Rh has not been proved to occur naturally.

It may be said, rather loosely, that all blood-group antigens are dominant mendelian characters—in respect of their equivalent antibody. Several of them are better described by the genetical term " intermediate characters ", since the description of a character as a dominant means that two doses of the gene responsible (in the homozygote) have an effect indistinguishable from that resulting from one dose of the gene (in the heterozygote). In the case of the M and N genes there is quite a marked dosage-difference. The erythrocytes of an N (NN) person contain more N substance than do those of an MN person (Landsteiner & Levine, 1928). This effect is also marked in the case of the Rh genes c (Race

Taylor, Boorman & Dodd, 1943), and C^w (Race, Mourant & Callender, 1946), and e (Mourant, 1945). It is perhaps wiser to avoid the terms dominant and recessive in referring to the blood-group antigens, for these terms are relative to the available antibodies. For example, if only the Rh antibody anti-C was known, then the C antigen would appear to be dominant to c, whereas if only anti-c was known then c would appear dominant to C. (Fisher's notation for the Rh antigens here used is explained below.)

As a general rule it seems that a blood-group gene produces an antigen, and this antigen is capable, under favourable circumstances, of inducing its specific antibody. But there are examples of overlapping in the antigenic powers of the end-product of gene action. The gene A_2, for example, produces the antigen A_2, while the gene A_1 produces the antigen A_1 (Landsteiner & Levine, 1930). Yet the antigen A_1 reacts with two different antibodies α and α_1, while the antigen A_2 reacts only with the former of these. The Rh gene C^w produces the antigen C^w, and the gene C produces the antigen C; yet the antigen C is capable of inducing the formation of the antibodies anti-C and anti-C^w (Race, Mourant & Callender, unpublished observations). The understanding of such anomalies may have to await greater knowledge of the substances involved. Fundamental biochemical knowledge in this field, as Morgan (1944) pointed out in these columns, is at present very slight.

Immunization

The stimulation of blood-group antibodies in the circulation of a person lacking the equivalent antigen can occur in two ways: (i) A man, or a woman, may become sensitized by the transfusion of blood containing an antigen which they lack; (ii) a woman may become sensitized when pregnant with a foetus which has an antigen, inherited from the father, which she herself does not possess. Several of the immune antibodies to be described have resulted from both processes.

Dienst, in 1905, suggested that a mother might be immunized by the blood of her foetus and that this process might be a cause of toxaemia of pregnancy. Ottenberg was attracted by the same idea, and in 1923 further suggested that jaundice of the newborn might be due to "accidental placental transfusion of incompatible blood".

It was not until 1939 that immunization of a mother by a foetal erythrocyte antigen was proved to occur, when Levine & Stetson described a case of stillbirth complicated by maternal loss of blood. The mother (group O) was transfused with her husband's blood (group O). The transfusion was followed by a severe but not fatal reaction. Later an antibody was found in the mother's serum which agglutinated the cells of her husband and those of 83 out of 104 group O donors. Levine & Stetson concluded that the antigen responsible had been present in the foetus, inherited from the father, and had stimulated the formation of the equivalent antibody in the mother. On receiving the transfusion the mother's antibody had reacted with her husband's cells carrying the antigen. A year later, when Landsteiner & Wiener (1940) had announced their discovery of the Rh groups, the antibody found by Levine & Stetson was identified as anti-Rh. Early in 1941 Levine, Katzin & Burnham demonstrated the causal relationship between the Rh groups and erythroblastosis foetalis.

A single transfusion of blood containing a given antigen may suffice to immunize a recipient lacking that antigen, but more than one pregnancy is generally necessary before a woman becomes immunized by a foetal antigen, at any rate if the antigen is Rh. The various blood-group antigens will be discussed individually.

The Species Antigens

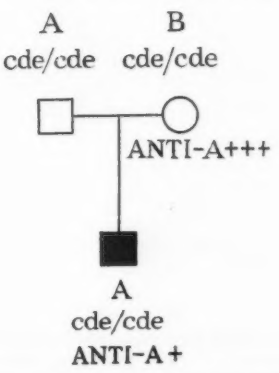
Several reports of 17th century transfusions (Wiener, 1943) describe symptoms due to the incompatible blood which had been given. Human recipients were given blood from lambs or sheep. The urine "black as soot" passed by the recipients was evidence of the effect of species agglutinins on the transfused blood. Had the claim of Mary Tofts, in the early 18th century (Sutton, 1943), that she gave birth to rabbits, not been discredited, one might have looked to her offspring for examples of haemolytic disease of the newborn due to species agglutinins.

The Antigens of the ABO System

The transfusion of blood containing the antigens A or B to patients whose serum contains anti-A or anti-B usually results in a severe reaction, often in a fatal one. Boorman, Dodd & Mollison (1945) have recently reported five such incompatible transfusions.

Iso-immunization to the ABO groups occurs in pregnancy. If a foetus has the antigen A or B, not possessed by the mother, then the titre of maternal anti-A or anti-B is increased. This was first demonstrated by Jonsson (1936) and has been confirmed by Smith (1945). The latter author demonstrated that in such "heterospecific" pregnancies the expected rise in titre of maternal agglutinins does not occur if the child is a non-secretor (that is, if the saliva of the child contains no A or B substance). In spite of this frequent immunization, haemolytic disease due to maternal anti-A or anti-B is almost unknown. The reasons for the protection enjoyed by foetal cells against these antibodies have been studied by Tovey (1945), who considers that several factors are involved, such as lack of placental permeability to anti-A and anti-B, neutralization of these antibodies by A or B substance in foetal plasma, lack of sensitivity of the foetal erythrocytes, and diminished activity of anti-A and anti-B at body-temperature.

FIG. 1. HAEMOLYTIC DISEASE DUE TO ANTI-A
(from Aubert, Cochrane & Ellis, 1945)



In this and the following pedigrees haemolytic disease of the newborn is indicated by a solid square (male) or circle (female).

Aubert, Cochrane & Ellis (1945) have reported a case of hydrops foetalis, which they attribute to maternal anti-A agglutinin. This is the only convincing example yet published of haemolytic disease caused by the ABO blood groups (Fig. 1).

The mother's serum contained a phenomenally large amount of anti-A (titre 1/16 million) and, what is particularly significant, although the baby was group A, it had strong anti-A in its serum (titre 1/128).

The Sub-groups of A

The possibility that a recipient of group A_2 may occasionally make α_1 when transfused with A_1 cells is considered by Wiener (1941). As far as I am aware no conclusive evidence has been produced showing that α_1 has caused either a transfusion reaction or haemolytic disease of the newborn.

The Antigens M and N

The presence of anti-M in the serum of a person of group N has been reported on about a dozen occasions. The majority of these antibodies were considered to be "naturally occurring" rather than immune. Wiener, however, describes anti-M in the serum of a patient of group N, thought to have been produced in response to a transfusion of M blood. As far as I know the only well authenticated case of anti-M causing a transfusion reaction is that of Broman (1944).

Singer (1943) described the first human anti-N agglutinin. It was found in the serum of a patient of group M who had been transfused with N blood (both donor and recipient were Rh positive). A reaction followed subsequent transfusion of N blood, but several pints of M blood were well tolerated.

A strong anti-N has recently been produced by a patient of group M who has shown remarkable powers of making antibodies (Callender & Race, 1946). The anti-N appeared in response to a series of very small (about 0·1 cm.^{3}) intravenous injections of N blood. In this case no anti-N was to be found in any of the very numerous samples of serum taken before the immunization. As far as I am aware neither anti-M nor anti-N has been blamed for haemolytic disease.

The Antigen P

Wiener & Unger (1944) reported anti-P agglutinin in the serum of a P negative patient. These authors considered that the antibody was made in response to transfusion. We have in our records five cases of anti-P agglutinin in human beings, but in none was there any good evidence of the antibody being other than "naturally occurring".

The Rh Antigens

Before discussing disease caused by the Rh groups it is necessary to give some key to this complicated system of antigens and antibodies. The Rh groups were last reviewed in these columns two years ago (Taylor & Race, 1944). Since that time several new facts have been disclosed and our understanding of the rather bewildering interaction of antigens and antibodies has been greatly helped by the ideas of Professor R. A. Fisher (Race, 1944; Fisher & Race, 1946). Briefly, Fisher, noticing the mutually antithetical reactions of two of the four types of sera known at the end of 1943 (Race, Taylor, Cappell & McFarlane, 1944), that is to say the 80% and 70% serum (Table I), supposed that these two sera were reacting with allelic antigens. One of these antigens Fisher called C and the other c. The two remaining antibodies did not give antithetical reactions, so the antigens which they recognized were not allelic to each other, though each presumably had an allele. The antigen reacting with the 85% serum was called D and that with the 30% serum E, and their hypothetical alleles were called d and e. Fisher pictured three closely-linked loci, each with two alleles, as responsible for the Rh groups, instead of one locus with seven alleles, as had previously been supposed. As an individual has two of each of the 24 different human chromosomes, he will have two of the Rh chromosomes, either of which may carry any combination of the three alternative pairs. For example, a person may receive CDe from one parent and cde from the other. This combination CDe/cde is the most frequent one in persons of Western European stock. Fisher's theory made several predictions which are gradually being confirmed, most notably by the

TABLE I. RH ANTIGENS AND ANTIBODIES (Race, Mourant & Callender, 1946)

ANTIBODIES		GENES AND ANTIGENS											
European bloods positive		R_o cDe	r cde	R_z cDE	R" cdE	R_1 CDe	R' Cde	Rz CDE	Ry CdE	C"De	C"de	C"DE	C"dE
70%	anti-C	−	−	−	−	+	+	+	(+)	−	−	(−)	(−)
85%	anti-D	+	−	+	−	+	−	+	(−)	+	−	(+)	(−)
30%	anti-E	−	−	+	+	−	−	+	(+)	−	−	(+)	(+)
80%	anti-c	+	+	+	+	−	−	−	(−)	−	−	(−)	(−)
(68%)	anti-d	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)
98%	anti-e	+	+	−	−	+	+	−	(−)	+	+	(−)	(−)
2%	anti-C"	−	−	−	−	−	−	−	(−)	+	+	(+)	(+)

The left upper compartment shows the interactions known before Fisher's theory was postulated. The middle compartment shows the extension demanded by Fisher's hypothesis, now in part confirmed serologically. The right and lower compartment shows the extensions made, and those suggested by the anti-C" serum. Reactions which have not yet been confirmed serologically are shown in brackets. Anti-C in this table means pure anti-C, and not anti-C + anti-C", which is the constitution of about half the sera called anti-Rh' by Wiener (1944). Wiener's notation for other antibodies is anti-Rh_o (anti-D), anti-Rh" (anti-E) and anti-Hr (anti-c).

discovery by Mourant (1945) of the predicted anti-e serum. Recently a third allele at the C-c locus, called C^w, has been found (Callender, Race & Paykoç, 1945 ; Race, Mourant & Callender, 1946).

FIG. 2. HAEMOLYTIC DISEASE DUE TO ANTI-D. HOMOZYGOUS FATHER

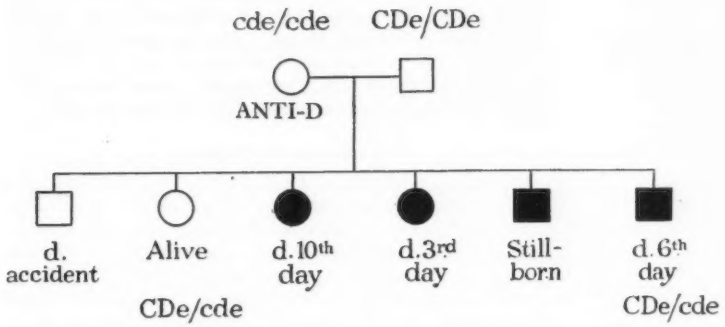
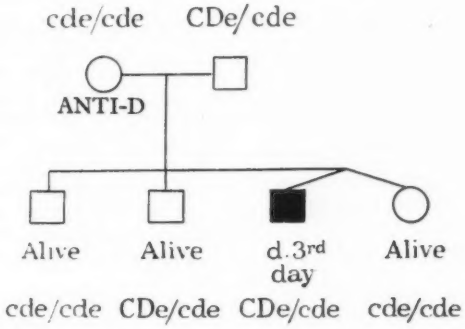


FIG. 3. HAEMOLYTIC DISEASE DUE TO ANTI-D. HETEROZYGOUS FATHER



The Rh Antigen C

Pure anti-C might be expected as a result of transfusing cDE/cde persons with CDe/cde blood, or when a woman of the former group has a child of the latter. For some unknown reason, however, anti-C has not been found except in the mixtures already mentioned.

The Rh Antigen c

Anti-c was described and its reactions were determined in 1943 by Race, Taylor, Boorman & Dodd. It is rare as a cause of haemolytic disease. Fig. 5 shows the pedigree of the St. family investigated by McCall (McCall, Race & Taylor, 1944 ; McCall & Holdsworth, 1945). Anti-c has been responsible for transfusion reaction (Callender & Race, 1946).

The Rh Antigen C^w

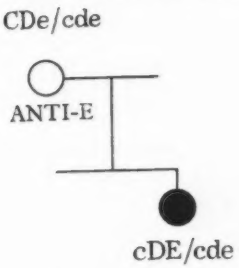
A recipient of Rh group CDe/CDe was given blood of group C^w De/CDe, suffered a mild reaction and made as a result anti-C^w (Callender, Race & Paykoç, 1945 ; Callender & Race, 1946). Anti-C^w alone has not yet been proved to have caused haemolytic disease. It has been found in the serum of mothers of haemolytic children, but in the presence of other antibodies such as anti-C and " incomplete " anti-D.

The Rh Antigen D

The antigen D is much the most important, clinically, of the Rh antigens. It is that discovered by Landsteiner & Wiener, and shown by Wiener & Peters (1940) to be a fairly common cause of reaction to transfusion. Levine, Katzin & Burnham (1941) proved it to be the main cause of haemolytic disease of the newborn.

The presence or absence of D makes a person Rh positive or Rh negative. The importance of D above other Rh antigens depends on its greater efficiency in stimulating the production of antibody, for anti-D is found more frequently than all the other Rh antibodies put together. Since 1940 this antibody must have been proved responsible for haemolytic disease in many thousands of families. Fig. 2 and 3 show two pedigrees from our records, the former with a father homozygous in respect of D, and the latter with a father heterozygous in this respect. Mothers with husbands of the Rh groups shown in these two figures sometimes make anti-D only, sometimes anti-D + anti-C, and very occasionally anti-C + the " incomplete " or " blocking " form of anti-D. Frequently the " incomplete " form of anti-D alone is made, and sometimes a mixture of anti-D + " incomplete " anti-D. The first child, or the first two children, are nearly always unaffected in a family with haemolytic disease due to the Rh factor. Levine (1945) has shown that when the first child is affected the mother usually has a history of past blood transfusion.

FIG. 4. HAEMOLYTIC DISEASE DUE TO ANTI-E



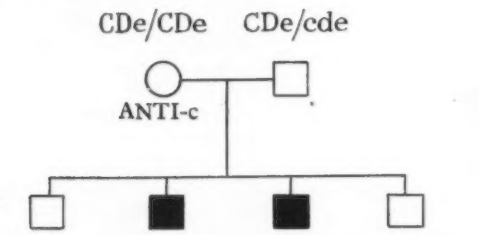
The Rh Antigen E

We have several examples of transfusion reactions due to this antibody. Fig. 4 shows a family in which pure anti-E caused haemolytic disease. In appropriate matings anti-E is sometimes found together with anti-D.

The Rh Antigen e

Until the discovery by Mourant (1945) of the anti-e serum the antigen e was in the position still occupied by d, the presence of which in a blood is detectable only as an absence of D. Mourant found the anti-e in the serum of a patient cDE/cDE who had been given many transfusions with increasingly severe reactions. Transfusion with cDE/cDE blood was completely successful.

FIG. 5. HAEMOLYTIC DISEASE DUE TO ANTI-c (from McCall, Race & Taylor, 1944; McCall & Holdsworth, 1945)



The Lutheran Antigen

This antigen, present in about 1 in 12 of the English population (Callender, Race & Paykoç, 1945; Callender & Race, 1946), has caused the formation of the corresponding antibody, anti-Lutheran, in a recipient of blood transfusion. It is not known whether it has the power to cause a reaction, for Lutheran-negative blood was used for subsequent transfusions of this patient. The Lutheran antigen is apparently not connected with any of the known blood-groups.

The Kell Antigen

Another antigen, "Kell", which also seems not to be connected with any of the known blood-groups, has probably been responsible for haemolytic disease of the newborn in the family shown in Fig. 6 (Coombs, Mourant & Race, 1946). The mother, who was "Kell"-negative, had in her serum an antibody which agglutinated the cells of her children, her husband, and about 7% of random bloods. The baby's cells were shown by the rabbit anti-human-serum serum test (Coombs, Mourant & Race, 1945) to have been sensitized *in utero*. The baby was severely anaemic, but not jaundiced, and responded well to a blood transfusion.

Miscarriages

The important paper of Levine (1943) on "Serological factors as possible causes in spontaneous abortions" has drawn attention to, and supports, the possibility first pointed out by Hirszfeld, that there may be a differential survival-rate depending on the ABO blood-groups of mother and foetus. It was found that more A children resulted from A × O matings, when the mother was A, than when the mother was O. [102 families of these two types of mating, grouped at the Galton Laboratory, failed to show this difference however (Taylor & Prior, 1938; Race, Ikin, Taylor & Prior, 1942). Further, a series of 112 bloods sent to this laboratory from mothers who had had early miscarriages shows no obvious disturbance of ABO group frequency (Woodward & Race, 1946.)]

Anti-Rh and the ABO Groups

In the same paper Levine notes for the first time the curious fact, which still lacks adequate explanation, that matings which result in the production of maternal anti-Rh are far more often compatible, or homospecific, on the ABO system than are normal matings. This has been the persisting experience of the Galton Laboratory and of Professor Cappell's and Dr. Plaut's departments. There is no possible doubt about the statistical significance of these findings.

Toxaemia of Pregnancy

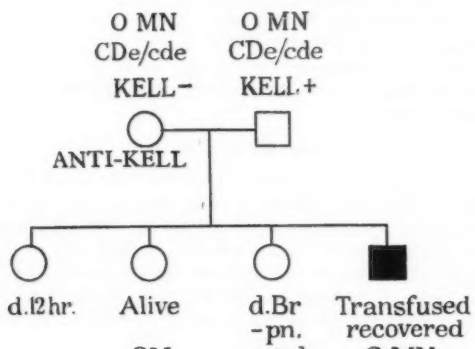
The question raised by Dienst, over 40 years ago, as to whether blood-group incompatibility between mother and foetus is a cause of toxaemia of pregnancy, still seems to remain without definite answer. Dr. Marjory McFarlane has kindly allowed me to quote the following unpublished figures. Of 59 Dundee women suffering from severe toxaemia of pregnancy, 34 were group O, 15 group A, 7 group B, and 3 group AB. This does not differ significantly from the normal Scottish distribution, and the same can be said of the Rh groups, there being 47 Rh positive and 12 Rh negative.

Rh and Mental Deficiency

Two groups of workers in the United States, Yannet & Lieberman (1944) and Snyder, Schonfeld & Offerman (1945), found an apparently significant distribution of Rh groups in "undifferentiated" mental defectives and their mothers, too many of the mothers being Rh negative.[1] On statistical grounds, Professor Penrose (personal communication) has thrown doubt on the significance of these findings, and work is now in progress which, so far, supports Penrose's views.

The blood-group genes are not known to exert other effects on the carrier, though there are theoretical reasons for thinking that this may occur. The blood-groups have so far

FIG. 6. THE KELL FAMILY (from Coombs, Mourant & Race, 1946)



[1] See the leading article in the *British Medical Journal*, 1945, 2, 188.

been shown to be capable of causing two disease states: reaction to transfusion can be due to the ABO or the Rh groups, and haemolytic disease of the newborn is almost invariably due to the Rh groups.

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[1] [*see BMB* 431]

[2] [*see BMB* 435]

MATERNAL RUBELLA AS A CAUSE OF CONGENITAL DEFECTS

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In the first six months of the year 1941, Gregg (1941), an ophthalmic surgeon of Sydney, Australia, saw an unusual number of infants with congenital cataract almost amounting to "a mild epidemic". The majority of the mothers of these children gave a history of an attack of rubella during pregnancy, and he found that the early periods of their pregnancies "corresponded with the maximum intensity of the very widespread and severe epidemic in 1940 of the so-called German measles". Furthermore, in his opinion, the cataracts did not "exactly correspond to any of the large number of morphological types of congenital and developmental lenticular opacities that have been described".

Actually 13 infants having congenital cataracts came under his own care and 7 others under that of his colleagues; moreover, he knew that similar cases had occurred during the same period in widely separated parts of Australia. He therefore communicated with colleagues in New South Wales, Victoria and Queensland and altogether was able to collect 78 cases. The cataract was usually bilateral, but in 16 instances it was monocular; in 10 of these infants it was associated with microphthalmos, and in a few cases there was also a corneal haze.

Frequently the babies were small in size, ill-nourished and difficult to feed, and 44 of them also suffered from congenital heart disease. In 68 instances the mother gave a history of rubella during pregnancy, and in the majority the illness occurred in the first or second month of pregnancy. A majority of the mothers contracted the disease in July or August 1940, and in the remainder the time of incidence of the disease was spread over the period December 1939 to January 1941. Returns from hospitals in Sydney showed that the peak of the epidemic occurred from the middle of June to the early part of August 1940. In 26 instances, out of a total of 35 mothers in which the record was available, the affected children were first children, and it was the young

adult group to which these primiparae belonged which was particularly affected by the epidemic. Gregg thought that this 1940 epidemic of German measles "differed greatly from the ordinary virus infections bearing that name". He said that he had never seen such severe examples of the disease or such severe complications; adenopathy, sore throats, involvement of ankle and wrist joints and the general constitutional symptoms were all very pronounced, and the rash was pleomorphic, being "macular, morbiliform, scarlatiniform and toxic erythematous". Co-incidentally with this epidemic there also occurred in military camps epidemics of sore throats, which spread to the civilian population.

All these points made Gregg wonder whether the illness was or was not rubella, but he came to the conclusion that it really was that disease and even speculated as to the possibility that the few mothers of infants with congenital defects who failed to give a history of rubella in pregnancy had suffered from mild attacks which had been overlooked. Although there is no definite statement to the effect that congenital defects are particularly prone to occur in severe epidemics of German measles, such a condition of affairs is certainly implied in this and other papers on the subject; it would, therefore, seem somewhat illogical to claim that attacks of rubella so mild as to pass unrecognized were also responsible for such defects.

South Australian Survey

Impressed by Gregg's findings and knowing that similar cases had occurred in South Australia, Swan of Adelaide and his colleagues conducted a survey which was supported by the National Health and Research Council of Australia. They have reported their results in a series of papers (Swan, Tostevin, Moore, Mayo & Black, 1943; 1944; Swan, 1944). For the purpose of this survey, they issued a questionnaire to general practitioners in South Australia and also asked for permission, if the mother lived in Adelaide, to question her about her past medical history and, if a pregnant woman was known to have rubella, to be allowed to see her and to follow her progress through pregnancy until the birth of her child.

The cases investigated occurred in the years 1939 to 1943, but it was not until 1942 that the "follow up" method was used; previously the enquiry had been a retrospective one. In all they collected information concerning, or examined, 74 mothers; the diseases from which they suffered during pregnancy and the numbers of their offspring who had congenital defects are shown in the following table:

Mothers	Disease	Infants with defects
57	Rubella	40
1	Rubella and measles	1
2	Rubella and mumps	0
1	(?) Rubella and (?) measles	0
7	Measles	0
1	Mumps	1
1	"Influenza"	1
4	None	4
74		47

The defects found were defects of the eye and heart, deaf-mutism, mental retardation, etc.; moreover, there was often more than one defect in the same child, and many of the children were under-developed and difficult to feed. Evans (1944), working on the same material, described dental defects.

As a result of their survey, these investigators came to the conclusion that "when a woman contracts rubella within the first two months of pregnancy it would appear that the chances of her giving birth to a congenitally defective child are in the region of 100%, and if she contracts it in the third month about 50%".

Welch (1945) has collected the numbers of congenitally deaf children born in New South Wales for each year from 1931 to 1941; in only one year, 1938, did they reach double figures, when they were 47, the mothers of 34 of whom developed rubella during the first four months of pregnancy. An interesting point in this connection is that this large number occurred two years before the severe epidemic of rubella in Australia, referred to above.

Observations in Britain and U.S.A.

Subsequently to the original Australian observations, the association between rubella in the mother and congenital defects in the child was also noted in America and England. The number of instances reported from America is not large, the largest series being reported by Erickson (11) (1944) and Albaugh (9) (1945). In England many paediatricians have seen isolated examples of the association, but by far the largest number of cases so far reported is that by Martin (1946), who, by means of a questionnaire, attempted to find the cause of deafness in deaf children who were born in the years 1940 and 1941, i.e. children born after the 1940 epidemic of rubella which was widespread and rather more severe than usual. Altogether she obtained particulars of 102 children, in 15 of whom the deafness was hereditary and in 8 followed meningitis, but 36 of the mothers, 20 of whom were interviewed, contracted rubella during the first four months of pregnancy and 6 others probably suffered from the disease.

Multiple Defects

In a number of these children there was also a defect of the eyes, and in a few, of the eyes and heart. Weston Hurst (Swan *et al.*, 1943) explains the not infrequent association in the same child of congenital heart disease and congenital cataract by assuming that the action of the virus is primarily on vascular structure and that cataract, for instance, follows interference with nutrition of lens fibres brought about by action of the aetiological agent on the hyaloid artery. In a histological examination of material from three fatal cases, Swan (1944) found evidence of an even more widespread attack on the tissues of the embryo, and pointed out that the restriction to the glomeruli of the lesions which he found in the kidneys supported Hurst's theory.

Some Difficulties of the Theory

The statistics given above constitute a strong prima facie case for the thesis that rubella in the early stages of pregnancy is likely to cause malformations in the foetus. Certain criticisms, however, must be answered satisfactorily, and further statistical studies are necessary, before the thesis can be regarded as proved. Obviously, the first question requiring an answer is whether the disease from which these expectant mothers suffered was in fact rubella. Although claims have been put forward that rubella has been transmitted to animals, these have not been generally accepted and there is, therefore, no specific serological test available. It has

been suggested that the presence of Türck cells in the blood can be regarded as a diagnostic feature in rubella, but this is an uncertain and unreliable sign, since these cells are also found in other conditions. The diagnosis, therefore, has to be made on clinical grounds, by the exclusion of other diseases which resemble rubella, and by any specific tests available for these exanthemata.

Swan and his colleagues state that exanthema subitum, erythema infectiosum, measles, scarlet fever and glandular fever might be confused with rubella, but that, except in a few cases, a detailed analysis of the symptoms of the mothers in their series failed to support any other diagnosis than that of rubella. Of the exanthemata mentioned by Swan *et al.*, scarlet fever and glandular fever are the most difficult to differentiate from rubella. As pointed out previously, epidemics of sore throats occurred in military camps in New South Wales in 1940, and these spread to the civilian population. Gregg (1941) thought that these were streptococcal in origin. Similar epidemics also occurred in South Australia ("Woodburn sore throat") in which the causal organism was *H. influenzae*, but in 1943, when Swan and his colleagues wrote their first paper, this epidemic had ceased, although congenital deformities associated with maternal rubella were still occurring.

Another difficulty in diagnosis is the fact that in rubella the rash is often so fleeting and the symptoms are so trivial that little notice is taken of the condition and a doctor is not consulted. The Australian observers, however, stressed the severe character of the 1940 epidemic, and the epidemic in Britain in that year showed more severe symptoms than is usual in epidemics of this disease. According to Weston Hurst (personal communication), the reason for the severity of the disease in Australia, and for the occurrence of so many cases in young married women, was the long freedom of the Australian population from epidemic rubella with the result that a large number of primiparae were at risk. In his opinion, it was the exposure of this large number of non-immune pregnant women to the infection which made recognition of congenital defects in their babies inevitable, and he is convinced of the association between the two conditions; moreover, he quotes as evidence of the severity of the disease the fact that half his staff at the Institute of Medical and Veterinary Science, Adelaide, which was predominantly a young one, were away with the disease at one time.

The change in the type of rubella may have been due to the development of a new capacity by the virus, or the epidemic might even be a new virus disease, but it is much more likely that the change was determined by the unusual opportunity presented by the presence of a large adult population susceptible to the infection.

A second question is why a disease which is so often so mild in the adult should produce such disastrous effects in the foetus? The answer given is that in mammals embryonic tissue is more susceptible to infection than adult tissue; moreover, this susceptibility is most marked in the early stages of development, and it is with the occurrence of rubella early in pregnancy that deformities have been found to be associated. A weak point in this argument, however, is the fact that the Australian workers found that other virus diseases—measles in particular—did not produce these deformities, although there is always the possibility that the effect of the more severe virus infection was to produce abortion.

Two other criticisms of the Australian investigations have been made; first, that in most of the recorded cases the enquiry as to the occurrence of rubella during pregnancy was retrospective, having been made when a congenital deformity was found in the newborn child, and that there are only scanty data concerning mothers who had rubella during pregnancy but gave birth to normal children. Swan and his colleagues did, however, examine a few cases non-retrospectively (positively, to use their phrase), and also found that 17 expectant mothers who developed rubella gave birth to normal children.

Secondly, the effect of other virus diseases on the expectant mother has not been adequately investigated, although in the Adelaide series the children of 7 mothers who suffered from measles during pregnancy were normal.

The available evidence supports the view that the Australian epidemic was due to rubella and, apart from the number of cases they collected, the most important and suggestive facts observed by the Australian investigators were, first, the important epochs in the development of the organs in which abnormalities were found—eyes, heart, teeth—are in the early period of pregnancy, just at the time during which it is stated that their mothers contracted rubella; secondly, congenital abnormalities were not found in the offspring of those mothers who had measles in early pregnancy.

There are no statistics available to show whether or not in the years following the 1940 rubella epidemic in England and Wales there was any increase in congenital malformations which are compatible with life. As far as deaths from malformations are concerned, there was no increase in children under 4 weeks nor from 4 weeks to 12 months in the year 1941, i.e. the year following the epidemic.

Statistical investigations to confirm or refute the association between maternal rubella and congenital deformities are difficult to carry out adequately because large epidemics are infrequent and the section of the population at risk on which they have to be carried out is a small one; indeed, it has been estimated that to obtain a really good statistical result, it would probably be necessary to include in the survey all the married women in England and Wales. A recent investigation in Milwaukee, Michigan, by Fox & Borten (1946), illustrates the difficulty in obtaining a sufficient number of cases and is also interesting in that, although the number of children investigated was small, the results obtained did not support the Australian thesis. In the city of Milwaukee, which has over half a million inhabitants, there is an epidemic of rubella about every ten years, and in the last twenty years there have been 44,482 cases of the disease. The investigators paid particular attention to the 1942-43-44 epidemic, with the following results:

	1942	1943	1944
Total number of cases	3,998	17,703	525
Total number in married women	73	477	31
Total number of married women investigated	19	122	10
Number of babies born to these women ...	1	9	1

Five of the mothers of the babies had rubella in the first 2 months, four in the 2nd-4th month, and one each in the 7th-9th month of pregnancy. Although one mother who had rubella at the end of the 1st month of pregnancy was delivered of a hydrocephalic still-born baby, there was not a single example of congenital deformity amongst the eleven babies,

and an interesting thing is that one mother who contracted rubella in the 2nd month of pregnancy produced a normal baby, whereas in a previous pregnancy her baby had bilateral cataract.

Conclusions

Rubella is not a notifiable disease in England and Wales, although it has been notifiable in the City of Manchester for some years, and it probably would be a help in the solution of the problem under discussion if it were, at any rate, in married women, made universally notifiable. Second attacks of rubella are rare, and therefore the Australian investigators suggested that pooled or adult serum might be used to confer passive immunity upon the expectant mother who had been exposed to the disease. The use of gamma globulin has also been suggested, but even more potent would be the gamma globulin fraction of rubella convalescent serum. The period of passive immunity is, however, short, perhaps not more than 2-3 weeks, and the injections would have to be repeated either until the woman had reached the 5th month of pregnancy or until there was no longer any risk of infection, whichever were the shorter period.

None of these preparations is available in Great Britain, and it therefore follows that the expectant mother should be guarded from exposure to the risk of infection with rubella, and perhaps of infection with other exanthemata also. There is, of course, one obvious practical drawback to any method or prevention or treatment, namely, that the ill-effects of rubella are produced, if at all, in the early weeks of pregnancy, and the mother may well be exposed to or even develop the disease before she realizes that she is pregnant.

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NOTE.—In a letter received by the author since this paper was written, Gregg states that he has seen or collected an additional 138 cases, 130 of which were in the year 1944, making a total of 206 examples of this association between maternal rubella and congenital defects. In the group of 130, the distribution of the defects was as follows :

Cases	Deaf-mutism	Congenital heart disease	Eye defects
85	present	—	—
17	present	present	—
5	—	present	—
6	—	—	present
8	—	present	present
8	present	present	present
1	present	—	present

SOME APPLICATIONS OF PRENATAL NUTRITION TO INFANT DEVELOPMENT [1]

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The development of the infant depends upon the development before birth, the one is continuous with the other. A child that is healthy at birth is likely to continue in health in its postnatal life. There are two main prenatal factors, the genetic and the nutritional, which will impair the chances of survival or improve the health of the infant. This paper deals with the nutritional. A cardinal difference is that these latter can be controlled, but the former, once the ovum is fertilized, are at present beyond our control.

Biological experiments on this subject have been mostly performed upon animals and confirmation upon the human subject is limited, largely by reason of the general difficulty associated with human experimentation, which is intensified in this case by the interesting condition of the subject.

Birth-weight

The infant at birth in health has lived and grown *in utero* on food supplies which have reached it from the mother across the placenta. Its curve of growth is not normal but is steep in the last three months of intrauterine life, more than two-thirds of the birth-weight being deposited in the last eight weeks. Three-quarters of this birth-weight is

[1] Lecture delivered at the Institute of Child Health, Great Ormond Street, London, 10 May 1946.

TABLE I. COMPOSITION OF THE HUMAN FOETUS IN GRAMS

	Body	Water	Protein	Fat	Ash
End of 5th lunar month –	300	260	22	3·5	1·5
End of 7th lunar month –	1,000	800	100	25·0	30
End of 10th lunar month (birth) – – – –	3,200	2,420	400	350·0	90
Average of daily deposition:					
1. Throughout foetal life –	11·4	8·6	1·4	1·25	0·32
2. In last 3 lunar months –	26·2	19·3	3·57	3·87	0·71
3. In last month – –	35·7	23·6	6·4	6·4	2·0

water. The daily rate of deposition is shown in Table I, where it is seen to rise steeply in the last part of pregnancy, the average daily increase being 11·4 grams a day throughout pregnancy and 35·7 grams in the last month.

Pronounced depletion of the maternal food supplies lowers the birth-weight (rats: Zuntz, 1919; guinea-pigs: Paton, 1903; rabbits: Reeb, 1905; sheep: Hammond, 1932). Moderate underfeeding, however, does not decrease the birth-weight (sheep: Hammond, 1932; cow: Eckles, 1919; gilt[1]: Hogan, 1928).

The best and most recent work is that of Wallace (1944, 1946). He fed pregnant sheep on diets which maintained weight, restricted (low-plane) diets, and high-plane diets of concentrate and excess rations. His results are summarized in Tables II and III.

TABLE II. INFLUENCE OF HIGH-PLANE AND LOW-PLANE DIETS IN LAST 8 WEEKS OF PREGNANCY ON BIRTH-WEIGHT AND POSTNATAL GROWTH (Wallace, 1944; 1946)

Diet	High-plane	Low-plane
Effect on ewe weight, pounds – –	44 (gain)	— 11 (loss)
Birth-weight, pounds – – –	10·4	6·8
Milk yield in 3rd week, pounds –	50	30
Milk yield over 16 weeks, pounds –	443	292
Lamb weight at 16th week, pounds –	72	56
Temperature-control at birth – –	Present	Absent
Neonatal mortality – – – –	Nil	High

Wallace demonstrated that the diet in the last eight weeks of pregnancy was important in that it not only raised or depressed foetal growth, but a high-plane diet also caused mammary-gland growth yielding a high milk-yield, of which the more vigorous lamb took full advantage. Still more important was his demonstration that the restricted rations not only depleted tissue-growth but also retarded physiological development, as shown by absence of temperature control and high mortality in neonatal life. The effects of restricted diets were more pronounced with twin births.

In the occupied European countries there has also been observed a corresponding decrease in birth-weights and increase in neonatal mortality. There was, however, a decrease in pregnancy toxaemia, which accords with Wallace's observation that low-plane diets produce increase of liver fat. In Britain, the moderate restrictions of diet due to the war did not lower the birth-weight (Huggett, 1944).

[1] A young sow.

Hammond (1932) has also shown that, with a low plane of nutrition, such that the ewe is ill-nourished at birth, the weight of individuals in twin or triplet lambs is definitely impaired. The result is that ratio

$$\frac{\text{weight of single lambs}}{\text{weight of individual twin lambs}}$$

is proportional to the degree of nutritive impairment. He inferred that in general the chance of survival was inversely proportional to the value of this ratio. Applying this ratio to the birth-weights in London in 1938-1939, and in 1941 and 1942, there is actually an indication of improved health and chance of survival.

The birth-weight is dependent not only upon breed (Eckles, 1919) and food supply of the mother, but also upon the demands of competing metabolisms for the food supply. The main competitors are other animals in the litter, e.g. twins, triplets or multiple litters; the metabolism of the mother if still growing, and finally the placenta itself. In sheep, individual members of twins are 23% and of triplets are 30% lighter than singletons (Hammond, 1932). In general, the size of individual young at birth is inversely proportional to the number in a litter in the pig, guinea-pig, rabbit and rat.

Curiously enough, the ratio is smaller for male than for female lambs. Hammond regards this as suggesting that males stand a better chance of survival than females. There is no known explanation for this based upon the actions of the sex hormones.

TABLE III. COMPARISON OF EFFECTS OF HIGH-PLANE (H.P.) AND LOW-PLANE (L.P.) DIETS IN EARLY AND LATE PREGNANCY UPON THE FOETAL GROWTH AND UDDER DEVELOPMENT (Wallace, 1944; 1946)

	Group 1		Group 2	
Diet of ewe in 1st 4 weeks – –	Maintenance		Maintenance	
Diet of ewe in next 9 weeks – –	H.P.		L.P.	
Diet of ewe in next 8 weeks – –	½ H.P.	½ L.P.	½ H.P.	½ L.P.
Average foetal weight (pounds)—				
At 56th day – – – –	1·7	1·7	1·7	1·7
At 144th day – – – –	11·3	6·5	11·1	5·8
Udders—glandular growth – –	+++	+	+++	+
Fat in liver – – – –	+	+++	+	+++

The competing effect of the maternal metabolism is shown by the influence of the weight of the ewe at birth on the weight of her lambs—as she gets older their average birth-weight rises. In Suffolk sheep, with young ewes the average twin weight is 11 pounds [5 kg.], and with adult ewes the average twin weight is 12 pounds [5·5 kg.] (Hammond, 1932). The same effect is seen in India, where the birth-weights from child-marriages are smaller than those from adults, and rise with increasing age of the mother.

The weight at birth influences the growth after birth (Marshak, 1936 ; Greene, 1931). Illingworth (1939) has drawn attention to the effect of low birth-weight in humans, and has shown that under modern conditions of civilization it may result in failure to attain normal weights. The work of Wallace (1944, 1946) shows a reason for this imperfect growth after a low birth-weight. The foetus on the restricted diet is equivalent to a premature animal without temperature control and poor in vigour and strength, which feeds at a poorly-developed breast yielding a poor supply of milk. Hess & Chamberlain (1927) have shown, however, that underweight infants can, with special care in feeding, attain normal weights in four years. This special care, however, involves prolonged dietary supplementation, organization and expense.

TABLE IV. BIRTH-WEIGHTS (POUNDS) IN LONDON IN 1938-1939, 1941, & 1942

Year	Mean birth-weight in singletons	Individual birth-weights of twins	Ratio of singleton weight to individual twin weight
1938-39	7·260	5·237	1·388
1941	7·125	5·125	1·390
1942	7·216	5·448	1·325

This raises the important question of whether the child who has been imperfectly nourished in prenatal life and has enjoyed a high plane of nutrition after birth can ever entirely recover vigour and health. It has been shown in the post-natal sheep (Hammond, 1932) and in the pig (McMeekan, 1940) that, after birth, different organs and portions of the body have different ages of optimal growth. Bone grows first, then muscle and then fat. Bone-length is an earlier growth than bone-breadth. If, therefore, the lambs start, say, on a low plane of nutrition, and are later put on to a high plane, their recuperative powers are limited mainly to those tissues growing mostly in the later period. The bodily proportions are therefore different to those of animals continuously on a high plane of nutrition. It was found, further, that there is some permanence of these effects of nutrition on body proportions (McMeekan & Hammond, 1940).

Wallace (1945) has shown a similar result during foetal life. Low-plane foetuses contrasted with the foetuses of mothers on a high-plane diet, had a differential impairment of tissue- and organ-growth, the nervous system being least affected, bone more so, muscle and flesh most. The alimentary canal was less affected than the heart, lungs, and kidneys, and the thymus, spleen, and liver were most depleted by low rations in pregnancy.

The Theory of Partition of Nutrients

It is desirable to know how the foetus is relatively successful in maintaining its body-weight, and the individual tissues apparently maintain themselves against under-nourishment, when the maternal food is in short supply.

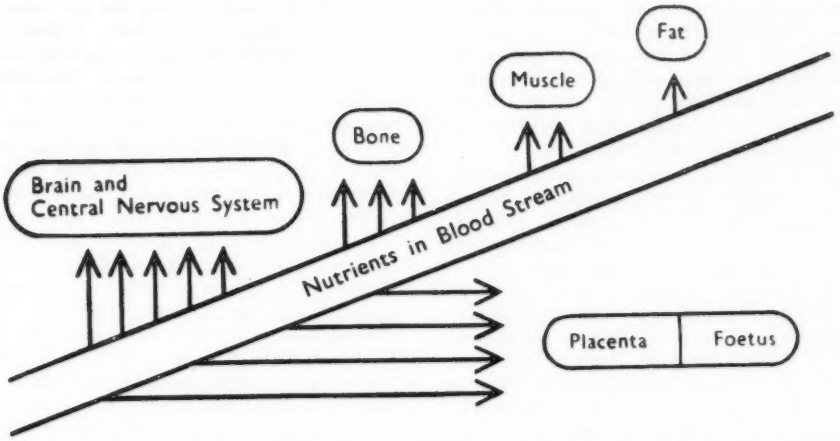
Hammond (1944) has proposed the theory of partition of nutrients, which states that the tissues having the highest metabolic rates have a priority of supply of all nutrients over those tissues and parts with a lower metabolic rate. This view was first developed by Child (1920), who first held that in different tissues of an organism there is an axial pattern of function which involves, amongst other things, a gradient of oxygen consumption correlated chemically with external factors. This means that there is a division of foodstuffs in proportion to the metabolic rate of the tissues concerned, those with the highest rates having the highest priority. Child's thesis that the metabolic rate governs the supply of nutrients has been adopted by Hammond as the basis of his theory, and is supported by the demonstration that there is a correlation between the rates of growth in young animals and their chemical composition (McMeekan, 1940). To give one instance, after birth the first tissue to grow is the bone, followed by the muscle and the depot-fat. In the early stages the first lipids found are in muscles, and are intracellular lipids of high iodine value with great chemical activity, the " élément constant " of Terroine (1920). Later, after the optimum growth of muscle has passed, the lipids deposited are those which form the depot-fat. These are relatively inactive and with low iodine value, the " élément variable " (Callow, 1935). At this stage, the growth-rate for bone and muscle is low and the animal is fattening. A similar parallelism has not so far been demonstrated for the prenatal fat, but it is known that the metabolic rate in foetal tissues is higher in the embryo than in the adult.

Taking these facts into account, therefore, Hammond (1944) has suggested that in early life the high total metabolic rate of foetal tissues enables the foetus to compete successfully with the relatively low metabolic rate of the maternal tissues, and so to obtain its desired nutriment.

He illustrates this by Fig. 1, in which the number of arrows denotes the metabolic rate and tissue's growth. As the supply of nutrients is decreased, the number of arrows is reduced, first fat losing its one arrow, muscle being reduced to one, bone cells to two and brain to three and the placenta plus foetus to three arrows. With further reduction in food supplies the fat and muscle arrows may even be reversed, while bone and brain grow at still further reduced rates. At this stage the maternal tissues waste and lose weight. With ageing of the embryo, its metabolic rate falls and the foetus competes with less priority and with greater difficulty with the maternal tissues.

This hypothesis Hammond supports (1944) by several instances. The instance of the twin lambs at birth being individually 23% lighter than singletons is duplicated in humans. For example, in a comparable series in London, singletons at birth weighed 7·26 pounds [3·29 kg.] and twins 5·24 pounds [2·39 kg.] (Huggett, 1944). When the lambs were fed at the breast, the ratio of singleton- to twin-weights increased (signifying greater relative food shortage), but when the lambs were later weaned and fed on grass the ratio became smaller.

FIG. I. PRIORITY OF PARTITION OF NUTRIENTS ACCORDING TO METABOLIC RATE (Hammond, 1944)



The number of arrows indicates the relative metabolic rate of the different tissues and its satisfaction by a flow of nutrients from the maternal blood-stream.

This is still more evident with litters. In rabbits, litters of 8-11 had individuals averaging 45 g. birth-weight, but with only 1-2 young they averaged 95 g. (Wishart & Hammond, 1933). But if unlimited food was given to the mother it was not possible to increase the birth-weights of the large litters, and this suggests some type of maternal control.

The placenta is a competitor. In the human at full term it bears a ratio to the foetus of one quarter to one twelfth. Clearly, the larger the placenta the better the storage capacity in the middle trimester and the diffusion capacity in the final trimester, and so the greater chance of foetal survival. If we compare the ratio of placental weight to foetal weight (P/F), we find that it becomes smaller as the placenta loses weight and the foetus grows (Huggett, 1941b).

TABLE V. THE RATIO OF PLACENTAL TO FOETAL WEIGHT (P/F), AT DIFFERENT AGES FOR SINGLETON AND SIB FOETUSES (SHEEP)

Age in weeks	10	12	14	16	18	20	22
P/F single embryos	1·7	1·3	0·98	0·69	0·43	0·27	0·20
P/F sib embryos	2·3	2·3	0·10	0·78	0·50	0·31	0·22

Similarly at the 21st day of pregnancy in the rabbit, the average P/F ratio is 0·83 for litters of 8-14 embryos, but 0·71 for litters of 7 or fewer embryos (Huggett, 1929).

It seems therefore that the placenta can compete successfully with the embryos in mid-uterine life (before it shows the normal signs of physiological degeneration characteristic of late-uterine life), and the greater the competition for nutriment the more the disparity between the placental and foetal weights. Nutrient supply, however, is not the only factor controlling weight, since when individual cases are considered they show overlap in the ratios. We have, however, another case of Hammond's theory of partition of nutrients.

We can now consider other conditions which have been known for some time but which are all covered by the generalization of Hammond—namely, the effects of shortage of individual foodstuffs. Hammond applies his theory not only to the gross aggregate total of nutrients but also to any one individual nutrient. Of these one of the most striking is that supply of nutrients concerned with the development of the erythrocyte and provision of adequate haemoglobin.

The Development of the Erythrocyte

In 1931 a considerable body of work emerged which has altered our ideas concerning anaemia in infancy. Mackay & Goodfellow (1931) focused attention on anaemia in infancy by showing that 45% of breast-fed and 51% of artifically-fed infants in an orphanage—working-class population of London—showed anaemia at 12 months of age. This anaemia was accompanied by a big rise in morbidity. It was entirely relieved by the administration of iron, with an accompanying decrease in morbidity and increase in weight. The anaemia was associated with anaemia of the mother in 50% of cases; it was also a progressive condition in the first year of life, which, however, could be reversed by iron medication. It was aggravated or precipitated by any type of jaundice in the infant, by oedema, or by replacement of human by cows' milk, and was associated with birth-weight, in that small infants at birth grew relatively more rapidly than big infants and seemed to develop anaemia more easily.

Mackay & Goodfellow attempted to give extra iron to the pregnant mother with a view to assessing its effect upon the incidence of anaemia in the infant after birth, but the experiment broke down due to conditions beyond their control. However, the experiment was attempted with success by Strauss in 1933 under easier conditions. He investigated pregnant women in whom the maternal anaemia was very low, an average of 36% haemoglobin compared with 76% in the control cases. In both groups there was no significant difference at birth, but at 12 months the infants of the anaemic mothers had only 46% haemoglobin (controls

showing 67%) together with microcytosis and poikilocytosis. He demonstrated that administration of iron in good dosage to the mother during the last three months of her pregnancy not only relieved her anaemia but also gave a normal blood-picture in her infant 12 months after its birth. The infants of the treated mothers had 70% of haemoglobin compared with 46% in the infants of untreated mothers. Both groups had exactly the same average haemoglobin at birth. Iron medication of the mother had therefore had no elevating effect on the circulating foetal haemoglobin.

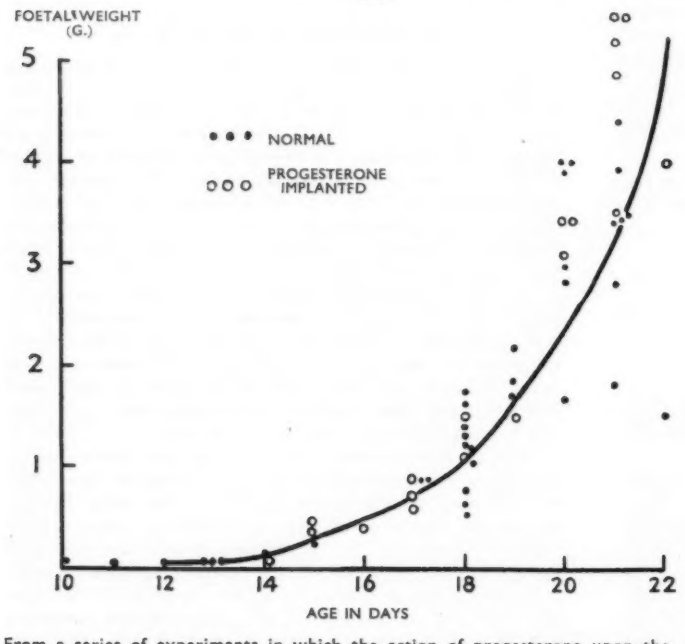
These observations of Mackay and of Strauss were confirmed by Smallwood (1936) in a parallel experiment in rats and humans. He showed that an iron-deficient diet for pregnant rats produced young with a normal haemoglobin percentage, but with a microcytosis at birth which rapidly developed into a hypochromic anaemia. In his parallel observations, the administration of iron to normal women in pregnancy, while causing no apparent change in the mother or her offspring at birth, did, however, markedly decrease the postnatal drop in haemoglobin. His colleagues Parsons, Hickmans & Finch (1937) carried this further and showed that, if the rats were kept for several generations on an iron-deficient diet, there was a greater anaemia, subnormal weight, and difficulty in rearing and reproducing when the young grew to adult size.

The presumption is that the lack of adequate iron supplies in pregnancy has depleted reserves in the embryo, which depletion reveals itself in the postnatal period when the diet is naturally short of iron. Two things lend weight to this surmise, first the demonstration by Zaleski (1886) that in the dog the liver of the embryo at full term has 391 mg. of iron per 100 g. of dry liver, compared with 43-78 mg. per 100 g. in the adult. In the human, at least two-thirds of this iron are stored during the last three months of intra-uterine life (Hugounenq, 1899). If there is a shortage, it is to be expected that this big storage might be defective without any signs in the circulating blood. That a shortage is normally liable to occur is evident from two things : first, that infantile anaemia can occur on a milk diet unless other sources of iron are supplied (Mackay & Goodfellow, 1931) ; second, the anaemia is worse on cows' milk than on human milk, which is to be expected since 1 litre of human milk has 3 mg. of iron and of cows' milk only 0·8 mg. per litre.

Fullerton (1937) has demonstrated, however, that in the human the liver is not the main store of iron. The human foetus has in its liver at birth only 50 mg. of iron, in other tissues 70 mg., but in the blood 330 mg. The position in the human embryo is clearly different to that in the dog foetus. Pommerenke, Hakin, Bale & Balfour (1942) have studied transmission of iron to the human foetus by " labelling " it with radioactive iron. It was given to the mother by mouth before delivery at term, and blood was removed from her and from the umbilical vein for estimation. It appeared in 40 minutes within the foetal circulation, which indicates a fairly rapid passage across the placenta at full term. In another series it was administered before therapeutic abortion in cases between the 2nd and 7th month of pregnancy. The radioactive iron was then estimated in the different tissues of the aborted embryo. The largest deposition was in the foetal erythrocytes, considerably less in the foetal liver, and negligible in other foetal tissues.

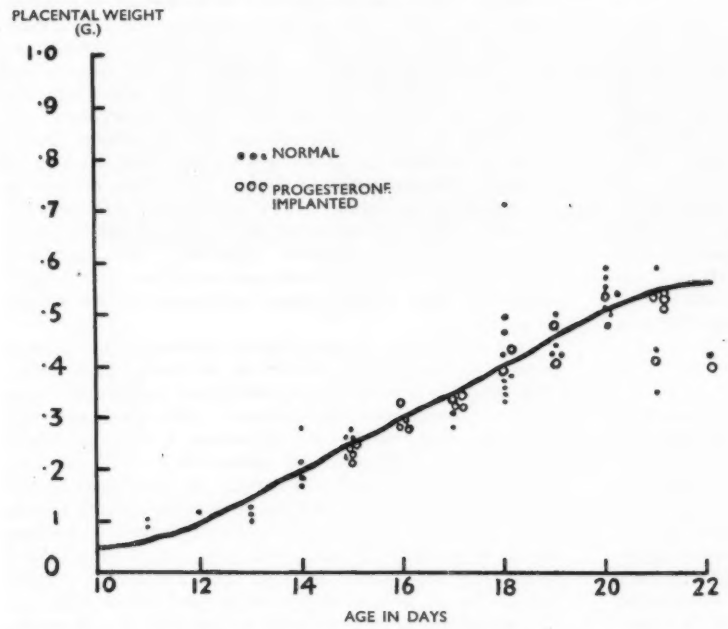
It is quite clear, therefore, that so far as iron is concerned, the total present in the diet of the pregnant animal or mother determines the severity and duration of the anaemia which occurs during the first year of life. Where there is a shortage, the mother shows an active anaemia of the hypochromic type and the infant shows no anaemia. Apparently the higher metabolic rate of the embryo has grasped the available iron at the expense of the low metabolic rate of the mother. This is, however, not the whole story, since, within the embryo, the circulating erythrocyte shows no deficiency at birth. Apparently, however, there must be a deficiency in the liver in the case of the dog. Fullerton (1937), as has been said, regards the reserves of iron for circulating blood as being the blood itself and such outside sources as are available to it in the postnatal food supply, since the haemoglobin percentage falls from 145 to 86 at the 9th month and as low as 37 in infantile anaemia. For this reason he stresses the necessity of iron feeding of the infant, and doubts the value of iron supplementations in diet of the pregnant woman. In view of the findings of Strauss and Smallwood, it is doubtful whether Fullerton's contention can be wholly correct.

FIG. 2. RELATIONSHIP OF FOETAL WEIGHT TO FOETAL AGE IN THE RAT



From a series of experiments in which the action of progesterone upon the foetal weight was assessed. The curve is the normal growth-curve for untreated rats. Note the rapid increase in the last two days. Full term is 21-22 days.

FIG. 3. PLACENTAL WEIGHT AT DIFFERENT DATES IN THE RAT



From the same series as the last. Note the marked slowing in the last two days of pregnancy. In many species (including the human), the placenta loses weight at this stage.

The development of erythrocytes is not, however, a matter only of iron. Wills (1931, 1933) has shown the megalocytic anaemia of pregnancy is curable by the administration of the haematopoietic factor of the liver or the extrinsic factor present in marmite [a vegetable concentrate]. This condition occurs in Indian women on a diet lacking the extrinsic factor. There is no record of the state of the blood of the infants born of the anaemic mothers, a matter of considerable importance. If the extrinsic factor be viewed in the light of Hammond's theory as a nutrient, for which the foetal haematopoietic tissues, with their high metabolic rate, successfully compete against maternal demands, the megalocytic anaemia of pregnancy in the mother is a logical sequence.

The same approach can be applied to minerals other than iron. Protein is a component of blood, both in the haemoglobin and in the circulating plasma proteins. In severe malnutrition the plasma proteins decrease. In pregnancy the mother stores much protein, both in her uterine and her extrauterine tissues. Protein needs to be increased in pregnancy for foetal requirements. This is recognized in all modern dietaries for pregnancy. Copper, likewise, is needed in the maturation of the normoblast to the erythrocyte. It is stored in the foetal liver in the pig (Wilkerson, 1934), and in both the goat and human (Ramage, Sheldon & Sheldon, 1933), so that at full term its concentration is double that of the adult liver. Unlike iron, however, copper is not deficient in the mother in pregnancy, the level of copper rising in the maternal blood from an average of 0·205% ±0·025 to 0·275% ±0·075 (Sheldon, 1932). In other words, a deficiency of copper is a factor less likely to cause postnatal anaemia in the infant.

Factors in Calcification

Calcium, on the other hand, with phosphorus and vitamin D, have been demonstrated as necessities which, if not supplied by the maternal diet in quantities above the normal non-pregnant adult requirements, will, because of the high demands of the foetal bone-growth, be inadequate not only for maternal metabolism but also for the postnatal development of the infant.

A decrease in the calcium and phosphorus in the diet of pregnancy causes no decrease in the embryo of the dog (Dibbelt, 1910 ; Zuntz, 1919), but even on a normal diet this is achieved at the expense of a loss of calcium from the maternal tissues (Sherman & Macleod, 1925), unless extra calcium and phosphorus be given (rat : Toverud & Toverud, 1929a ; human : Toverud & Toverud, 1929b ; Booher & Hansemann, 1931). Maternal caries (M. Mellanby, 1929) and osteomalacia (Maxwell, 1930) and, with the osteomalacia, intrauterine rickets, can also occasionally occur and are curable by cod-liver oil together with calcium and phosphorus. A rachitogenic diet in puppies can cause rickets more effectively if it is begun, as the maternal diet, in the intrauterine period (E. Mellanby, 1926). The Toveruds (1929) showed that while equilibrium is reached in the non-pregnant adult on a diet containing 0·7 g. of calcium and 1 g. of phosphorus, in pregnancy this needs to be raised to 1·6 and 1·7 grams respectively, while Sontag, Munson & Hoff (1936) brought forward evidence that, within limits, foetal ossification is independent of the diet, provided that adequate supplies of vitamin D are present. This confirms the findings of Abel (1931), who showed, however, that excess causes hardening of the foetal skull-bones.

It is clear, therefore, that the early high rate of metabolism of bone-growth *in utero* makes demands on the nutrients required, which are satisfied at the expense of the mother's tissues unless supplied in extra amounts in her diet. Further, if the supply is only partially met the infant shows signs of deficiency in post-uterine life. In the case of these nutrients, however, unlike iron, there is a rich supply in the maternal milk, provided that the diet of the mother in lactation is adequate. But the foundation is laid *in utero*.

What has been said about iron, calcium, and phosphorus applies also to all other nutrients in varying degree. The diet must be balanced in quality and adequate in all respects, with fortification in certain foodstuffs. It needs to be fortified for the mother's requirements, particularly with certain amino-acids such as methionine. At the moment we have no direct evidence of the necessity of these supplements for foetal development or for its postnatal life, though it would

be absurd to expect its requirements in growth to be less than the adult requirements.

It is necessary here to refer to three important experiments conducted on supplementation of the mother's diet during pregnancy. None was so complete, owing to the difficulties of human experimentation, as to be conclusive, but all three were significant. In South Wales and Gateshead it was found that supplementation with vitamins, milk and iron decreased still-births and neonatal deaths (Williams, 1939). Ebbs, Tisdall & Scott (1941) compared good diets with poor and with supplemented diets, and found that the addition of fruit, eggs, milk and wheat-germ decreased morbidity markedly, while in 1942 the People's League of Health showed that supplementation of normal diets with minerals and vitamins decreased prematurity and slightly increased birth-weight. All these effects were accompanied by improvements in the maternal condition during pregnancy.

Placental Permeability

In investigations of the placental permeability there is a limited number of observations which bear on the question of the postnatal development of the infant.

The most important is that it is normal for the placenta to show atrophic changes which, towards full term, result in approximation of the two blood-streams, with diminution and disappearance of the intervening layers in varying degree in different species (Grosser, 1925 ; Mossman, 1937). This results in a big increase in permeability in the last months of intra-uterine life, with a concomitant passage of the food-stuffs. This is well shown in curves relating the intra-uterine age to the foetal weight and the placental weight, and by the passage of radio-active sodium in different species of increasing permeability (Flexner & Gellhorn, 1942).

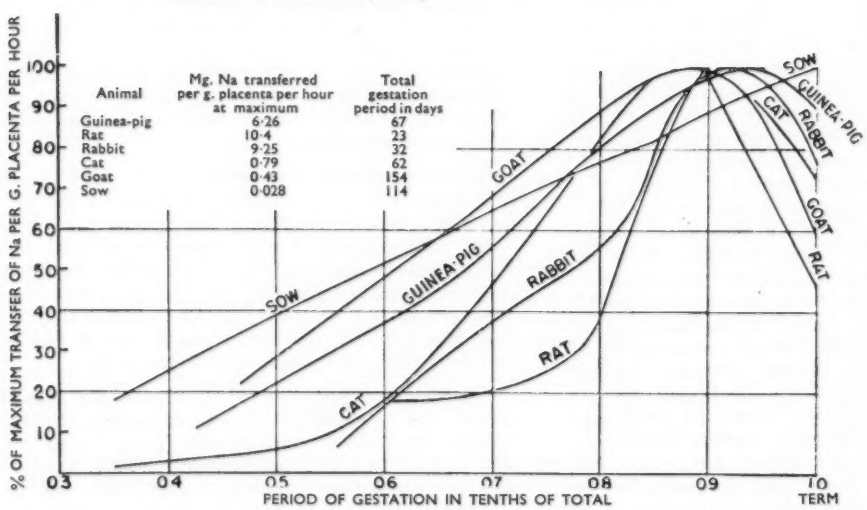
The second point of importance is that the passage of foodstuffs is often against the physical gradient of concentrations. This raises the question of mechanism of placental transfusion which, with molecular weights over 350, appears to involve mechanisms other than simple diffusion (Anselmino & Hoffman, 1929), and particularly so with colloids and particles. However, there is no doubt that in the last three months of intrauterine life the placenta becomes very permeable to certain organisms and certain colloids, though so far as the evidence shows, apart from lipids, none passes in nutritional quantities. In the case of proteins, the passage of nutritional quantities is by amino-acid diffusion (see Huggett, 1941a). Proteins can pass across in colloidal state, but only in " immunological " quantities. This applies to certain viruses, to certain toxins and antitoxins, and to agglutinins, the most striking being the passage of the Rhesus factors.

This passage of immunological quantities of proteins through the placenta is relevant to the known permeability of the placenta to traces of essential factors, notably the water-soluble vitamins and the hormones. The whole question, therefore, is of considerable importance in the nutrition of the infant. Variation in the permeability of the placenta in different individuals is suggested by two observations. In the first place, the incidence of erythroblastosis foetalis in Rhesus-positive infants of Rhesus-negative mothers should be 90-100%. In actual fact only 5% of these infants develop erythroblastosis foetalis. Haldane (1942) suggests that in only 5% of placentae is the permeability so great that the isoagglutinins can traverse to the foetus. Secondly, Dienst showed in 1905 that if the attached placenta at full term was perfused with methylene blue, the dye appeared in the maternal urine in only 20% of cases.

While in both these cases there are alternative explanations, the possibility of differential permeability affecting the nutritive supply of the infant at the stage when its reception of nutrients is maximal is an important aspect of the question of the influence of prenatal nutrition on postnatal development. What is required is the optimum flow of nutrients to attain vigour without extremes of weight.

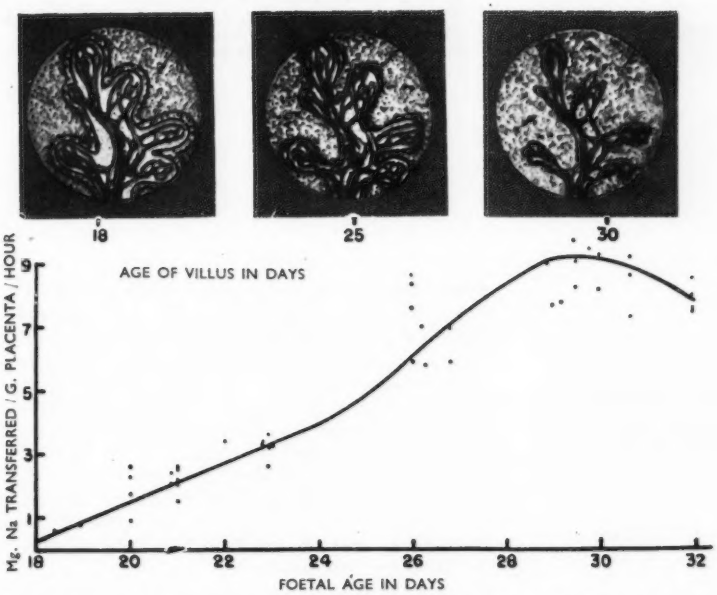
It is desirable here to draw attention to two points made by Barcroft (1944) in this connection. He emphasizes the importance of placental size and, secondly, of its opposition to oxygen passage, and ventures the opinion that the size of the foetus is limited by the size of the placenta and its opposition to oxygen passage. What limits the placenta we do not know.

FIG. 4. RATE OF SODIUM TRANSFERENCE ACROSS THE PLACENTA
(Flexner & Gellhorn, 1942)



This shows the relative placental permeability in different species at different dates during pregnancy.

FIG. 5. CORRELATION OF PERMEABILITY AND PLACENTAL STRUCTURE AT DIFFERENT AGES IN THE RABBIT.
(Flexner & Gellhorn, 1942)



The tissue intervening between the maternal and foetal bloods—decidua and trophoblast—atrophies in pregnancy in varying degree in different species (most in the rabbit) with an accompanying increase in permeability, with a change in the last tenth of pregnancy.

It must be admitted that we have no sure means of assessing the nutritive condition of the infant *in utero* either directly or through a study of the maternal condition. This is not surprising, as it has been shown that foetal death or removal without placental death does not remove the signs of pregnancy, which progresses to full term, resulting then in the delivery of the placenta, with the concomitant signs of puerperium (mouse : Newton, 1935 ; monkey : van Wagenen & Newton, 1943).

The nearest we can go is to recognize that maternal loss or subnormality of weight, or decrease in functional efficiency or decrease below the physiological normal for pregnancy (where known)—all or any of these stigmata are danger signs of a condition liable to impair the health of the foetus *in utero* or the infant after birth.

In conclusion, we can emphasize that a balanced diet in pregnancy, duly fortified where necessary, is essential for foetal and infant health, quite apart from the benefit conferred on the mother herself.

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BLINDNESS AND VISUAL DEFECT OF CONGENITAL ORIGIN

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The immense advances in public health administration during the past century, and in chemotherapy during the past decade, have greatly reduced the incidence of infectious disease generally and of ocular infections in particular. In consequence, other causes of disease have assumed a proportionately greater significance. This is strikingly seen in a comparison of the causes of blindness in children at different periods during the past sixty years.

Decline of Ophthalmia Neonatorum and other Infective Causes of Blindness

In 1884, the then newly-established Ophthalmological Society of the United Kingdom carried out a collective investigation on the causes of blindness amongst inmates of blind-schools and institutions for the blind. Ophthalmia neonatorum was found to be the responsible cause of blindness in 30-41%. These percentages cover inmates of all ages and, as the liability to blindness increases with age, it is clear that considerably more than 30% of blindness in children must have been caused by ophthalmia neonatorum.

In 1922, the Board (now Ministry) of Education found that, in the schools for blind children in England and Wales, 28·5% of the scholars had been blinded by this affection. A parallel survey carried out in 1944 showed that in the space of twenty-two years the proportionate incidence of blindness from ophthalmia neonatorum had declined to 9·2%. It is likely that within a decade blindness from ophthalmia neonatorum, once a dominant cause, will have become a rarity in the United Kingdom, for it is exceptional now for an infant to be blinded by this affection. In the four years 1941-44, only three babies in the whole of England and Wales have become blind from this disease.

Though no strictly parallel figures are available, there is much suggestive evidence that a decline of the same order as seen in ophthalmia neonatorum has occurred in other infectious eye diseases leading to blindness and visual defect. Congenital syphilis has declined greatly in frequency, and in consequence blindness and visual defects from this cause have also greatly diminished. Phlyctenular ophthalmia, too, has declined, and so has blindness from the various infectious fevers. As a result, the proportionate incidence of the different causes of blindness has become greatly affected. Whilst in 1922 congenital and hereditary lesions, including myopia, accounted for 37·3% of the causes of blindness in children, in 1944 no less than 67·6% of all blindness was produced by these affections.

In England and Wales the number of blind children between the ages of 5 and 16 has shown a steady decline since 1923. In that year the rate per 100,000 children in that age group was 36·4. By 1943 the rate had fallen to 20·3. Table I shows the decline as recorded at intervals during that period.

TABLE I. INCIDENCE OF BLINDNESS IN CHILDREN AGED 5-16 YEARS, ENGLAND AND WALES, 1923-43

Year	Population aged 5-16 years	No. of Registered Blind aged 5-16 years	Rate per 100,000	
1923	7,477,143	2,723	36·4	
1925	7,306,761	2,720	37·2	
1927	7,385,359	2,554	34·6	
1929	7,262,590	2,438	33·6	
1931	7,166,056	2,355	32·9	
1933	7,246,446	2,089	28·8	
1936	6,890,730	1,853	26·9	
1938	6,694,300	1,676	25·0	
1939	Population	1,619	24·2	Based
1940	figures not	1,499	22·4	on
1941	available	1,425	21·3	1938
1942	for	1,369	20·5	population
1943	publication	1,355	20·3	figures

That decline is, of course, to be explained mainly by the decline in the infectious causes of blindness. It carries this significant implication: as to-day some two-thirds of all blind children are afflicted from congenital and hereditary lesions, the rate of blindness per hundred thousand is likely to fall below the present 20·3, but within foreseeable time the rate will have become stabilized at the somewhat reduced level, for present-day methods of operation and treatment do not materially affect the congenital and hereditary lesions. A clear appreciation of the underlying factors in this group has therefore become of immediate and practical importance.

Terminology and Classification of Congenital Eye Defects

It is unfortunate that our very terminology of the congenital and hereditary lesions is confused. This confusion

reflects, of course, our ignorance of the scope of the problem. The term congenital blindness has no precise meaning. It is sometimes used as synonymous with a neonatal infection, such as blindness arising from ophthalmia neonatorum, or from birth injury; sometimes it is used to indicate a transmitted maternal infection, such as syphilis; and it is also used to designate blindness from genetic causes. By usage rather than by precise definition, blindness from such infectious disease as ophthalmia neonatorum and congenital syphilis is generally not included in assessments of blindness of congenital and hereditary origin. The tendency has been to confine the term congenital blindness to that arising from malformations and genetic infections. This, however, is not strictly valid, for there are other factors besides these two in congenital blindness. Nor may it be assumed that whatever be the case with malformations, blindness from genetic affections always manifests itself at birth. Such a characteristic genetic affection as retinitis pigmentosa may not cause blindness until well on in adult life, or even beyond.

An unsatisfactory terminology does in itself introduce confusion, but it is unlikely to be replaced until adequate knowledge throws up better terms. The first essential in any clear appreciation of the significance of the factors operative in congenital causes of blindness and visual defect is, therefore, a more detailed study of the group of affections that to-day makes up some two-thirds of all causes of blindness in children. As yet only tentative and indirect explorations have been carried out.

Suggestive data are obtained from an analysis of the causes of blindness in infants up to five years of age admitted to the Sunshine Homes for Blind Babies. During the period 1920-43, 600 babies were admitted to these Homes conducted by the National Institute for the Blind. No less than 261 (43·5% of the total) were blind from clearly-defined malformations or congenital affections. "Congenital anomalies" (not more clearly defined) were responsible for 78 cases. Frankly congenital malformations, such as microphthalmos and buphthalmos, accounted for 47 and 24 cases respectively. Cataract of congenital origin was responsible for 48 cases, whilst no less than 24 cases were due to glioma of the retina, presumably bilateral.

It is difficult to sort out from this mass those that were genetic from those that were maldevelopmental in origin. Moreover, it is possible that some lesions grouped as endophthalmitis of infective origin might be due to transmitted maternal infection, as it is also likely that some of the cases of optic atrophy not included in the group of congenital lesions, might be congenital in origin. A significant feature of the findings in this study is that only one infant is noted as blind from retinitis pigmentosa, a disease that is undoubtedly genetic in origin and, though not manifest at birth, must be considered as congenital.

It is obvious that the very limits of congenital factors of blindness and visual defect have not been defined. For the moment one can only fall back on more or less valid generalizations. It is possible to distinguish in broad outline the following groups:

1. *Malformations.* Congenital malformations have a wide anatomical range, extending from such a rare occurrence as congenital anophthalmos to relatively minor anomalies of the eye. Even the minor anatomical anomalies may have serious import. An abnormally-formed disc, or an ill-developed fovea, may cause gross visual defect. Most of the congenital anomalies have clear clinical features, as characterized by the names of microphthalmos, buphthalmos, coloboma iridis, coloboma of the choroid, coloboma at the macula, congenital cataract, subluxation of lenses, and other designations. Congenital nystagmus is in a category by itself, for often no anatomical defect can be observed, but it is possible that, in some cases at any rate, there is lack of development of the fovea.

The aetiology of all these conditions is obscure. In days gone by congenital syphilis was frequently blamed, and "intrauterine inflammation" served as an alternative aetiological diagnosis. That many of these cases are genetic in origin is obvious from the intensive genetic studies that have been published on these anomalies, but frequently no genetic basis can be established. There is lack of evidence in many cases of any dominant transmission, or of recessive manifestation; consanguinity is unusual, and a goodly proportion of these anomalies are "sporadic", even if each of these anatomical lesions has been observed as a genetic feature.

Though much work has been done on the experimental induction of ocular anomalies by changing the prenatal environment of the embryo, it cannot be said that experimental embryology has been particularly successful in elucidating the nature of these lesions. None the less, it is established that experimental congenital cataract can be induced by hypocalcaemia in the pregnant rat. Some evidence for a clinical parallel is also available.

One puzzling feature in these congenital ocular anomalies is their frequent association with systemic malformations. Subluxation of the lenses is apt to be seen in arachnodactily; aniridia may be associated with syndactily, and even lobster-hand and -foot. Macular coloboma in one particular family was associated with apical dystrophy of the hands and feet; in another family, anomalies of the skin and hair were present with macular dystrophy. Deficiency in dental enamel in cases of congenital cataract finds a ready explanation in the common underlying hypocalcaemia at a critical period in intrauterine development, but it is difficult to see a developmental basis for such a freak association as aniridia with lobster-hand and -foot, or macular coloboma with apical dystrophy of the terminal phalanges. Conceptions like status dysraphicus help to clarify the position somewhat in such conditions as arachnodactily, but it cannot be said that they do indeed throw much light. Genetic explanations, such as particular genes influencing a variety of characters, have much theoretical validity, but detailed knowledge of the multiple potentialities of genes is still sadly lacking. The confusion is not eased by the fact that known intrauterine infections can also exert widespread effects and produce weird combinations of anomalies.

2. *Abiotrophies.* In contrast to the gross anatomical changes seen in the congenital malformations, is the wide group of ocular lesions in which there are no structural anomalies at birth, but which are none the less determined congenitally. Retinitis pigmentosa has already been mentioned as an example of this group, but there are many other less-common affections of this type. The large group of macular dystrophies, the familial forms of chorôidal sclerosis, and the corneal dystrophies, are all well-established examples. A tissue that is apparently normal at birth, and may indeed function normally for a number of years (sometimes for a variable number in different families) shows dystrophic

changes, generally of a progressive character, and frequently ending in blindness. Both dominant and recessive forms of most of these conditions are recognized, and their congenital nature is obvious from their hereditary character. The designation of abiotrophy for this group of conditions has been criticized; the criticism is valid on etymological grounds, but not particularly helpful. It is of some importance to draw a sharp line of demarcation between the structural anomalies present at birth and the congenitally-determined affections.

The abiotrophies are probably much more common than is generally supposed. There is good reason for regarding the high degrees of pathological myopia as examples of abiotrophy. It is certainly a clinical fact that the complications of high myopia develop not at the time the myopia itself originates—in childhood and adolescence—but in late middle life, when there is no mechanical stress of growth to disturb the choroid and retina. Though the evidence is not conclusive, there is much to suggest that some forms of cataract and optic atrophy occurring late in life are essentially abiotrophic. It is arguable that some clinical conditions that are designated as senile degenerations of the eye are essentially late abiotrophic manifestations. Genetic evidence in support of this view is not difficult to obtain in almost any of the " senile degenerations " of the eye.

3. *Phakomatoses.* A group of conditions, of which tuberose sclerosis is a characteristic example, has features that link them with both the abiotrophies and neoplasms. A structure which is apparently normal at birth may develop changes which destroy both its function and the life of the patient. The tumours in tuberose sclerosis and neurofibromatosis behave in this manner; their effect is widespread and variable, as these tumours have a wide anatomical distribution. It is possible that so far only the more severe phakomatoses have been recognized, but that the condition, in its minor forms, with its minimal mother-spots (whence the name of phakomatosis), is common. The congenital origin of the phakomatoses is shown both by their genetic behaviour and by the congenitally-present phakomata.

4. *Neoplasms.* It is tempting to speculate on the relationship between the phakomatoses and the congenitally-determined (or congenitally-present) neoplasms such as glioma of the retina. As yet no close connection between the two has been established. None the less it is clear that glioma of the retina has a marked hereditary tendency with an irregular dominant mode of inheritance. A number of pedigrees extending over two generations has been published, and there is one on record extending over three generations. Glioma of the retina is estimated to occur once in every 33,000 births. The high mortality of these tumours presupposes a high mutation-rate to maintain equilibrium in distribution.

5. *The lipoid dystrophies.* Though relatively uncommon, these dystrophies are of considerable theoretical importance. Those having ocular implications are: infantile and juvenile amaurotic idiocy, Niemann-Pick disease, and Christian-Schüller disease. Like other abiotrophies, none of these is manifest at birth, but that they are congenitally-determined is shown by their genetic behaviour. The significance of the lipoid dystrophies lies in the fact that they form the one group of abiotrophies in which biochemical changes have been found, and in the case of the Christian-Schüller disease, these have indicated possibilities for therapeutic control.

6. *Intrauterine infections.* Apart from congenital syphilis, which is the classical example of a transmitted maternal infection producing widespread lesions present at birth, or supervening later in life, there are now at least two more recognized infections that are not held back by the placental barrier. Maternal toxoplasmosis can produce extensive changes in the nervous system of the offspring, as also a fairly characteristic central choroiditis which leads to blindness. More recently the virus of rubella has likewise been shown to be responsible for extensive lesions, of which congenital cataract and fundus changes are not the least striking.

The problems of intrauterine infection are fundamentally those of the environment of the growing embryo, and of the nature and variety of malformations that changes in such an environment may produce. To what extent minor lesions and functional derangements appearing later in life—as distinct from gross congenital anomalies—may also be caused by intrauterine infection must still be a matter of speculation.

* * *

If to-day some two-thirds of the causes of blindness in childhood are recognized as due to congenital and congenitally-determined causes, it must be admitted that there is little concrete knowledge as to the relative significance of the many causes of congenital and congenitally-determined disease. There is even less knowledge of the role of congenitally-determined factors in the development of anomalies later in life. A vast field of endeavour lies open. A century of effort has produced the present-day control of infectious disease. The exploration of the problems of congenital and congenitally-determined disease will require an effort no less intense, and the results may be commensurate.

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THE GENETICS OF CANCER

A Short Review of Experimental Findings

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The conception of an interaction of several factors in the genesis of the cancer process is not a new one, but it has received increasing support as a result of the researches of the last decade. Of these factors, genetic constitution has been shown to play an important part in animals, and there can be no reasonable doubt on general grounds that the conclusions drawn from animal experimentation are applicable in modified form to the pathology of human cancer. The genetic aspect of the cancer problem has been investigated in many laboratories, but the pioneer work of establishment of strains of mice with differing cancer incidence was done largely by American biologists and geneticists. The mouse has proved to be a valuable animal for these experiments, owing to its short life-span, its high reproductive rate, and its special susceptibility to a visible cancer, namely, of the breast.

Three difficulties arose in applying the Mendelian law to cancer :

1. No animal can be assumed to be cancer-free, whatever its age at death ; in other words, there is apparently no upper limit to the cancer age. This difficulty has been emphasized by Gorer (1937), who gives the following example : " Suppose we have three mice of which one dies of mammary cancer six months old, the second dies cancer-free at 15 months, and the third dies of mammary cancer at two years, what can we say of the genetic constitution of the cancer-free mouse ? " There seems to be no means of overcoming this difficulty, but the failure to recognize it invalidated much of Slye's work.

2. Mammary cancer strains do not group themselves into " high " and " low ". Incidences ranging from 0 to approximately 100% are described in genetically pure stocks. This fact in itself is sufficient evidence that mammary cancer cannot be caused by the action of a single gene. Thus comparisons must be based on populations, rendered as homozygous as possible by continued brother-sister inbreeding (Little & Gorer, 1943, p. 318).

3. Experiments involving crossing between high and low cancer strains always give the result that the F_1 mice derived from high cancer females show a high breast-cancer rate, whereas in the F_1 mice derived from low cancer females the incidence is low. This fact, first pointed out by Lathrop & Loeb in 1918, has been amply confirmed by other workers. A good summary of the position is given by Burrows (1945, p. 352), who points out that the degree of susceptibility in the offspring of a low-cancer strain mother crossed with a high-cancer strain father is passed on to the F_2 generation.[1]

Influence of Bittner's Milk Factor

The conclusion to be drawn is that the existence of one or more extra-chromosomal factors gives the female parent a much greater influence upon the offspring than that of the male. It seemed natural to seek this factor in the generative system, and though a considerable volume of work was done in transferring fertilized ova from the uteri of high cancer to low cancer mice, it soon became apparent that the extra-chromosomal influence lay in the milk (Bittner & Little, 1937). Since this time, a vast amount of work has been done, especially by Bittner, in an attempt to discover the nature of the " milk-factor " and the conditions under which it acts. A complete account of this work cannot be attempted here, but summaries are already available (Andervont, 1945b ; Burrows, 1945, p. 355). But the following well-established facts may be noted :

a. Females of all high cancer strains foster-nursed by low cancer mothers show reduction in mammary cancer incidence. The degree of reduction depends upon how soon after birth the babies are removed from their own mothers. There is some indication that reduction is maximal if the babies are removed from the uterus at term (Andervont & McEleney, 1941).

b. Females of low cancer strains foster-nursed by high cancer mothers show increase in mammary cancer incidence. The degree of increase varies with different strains and in different laboratories (Miller & Pybus, 1945).

c. Susceptibility to the milk factor begins to decrease after birth, but this can be overcome by giving a large dose—e.g. by using milk factor derived from dried mammary cancer tissue (Dmochowski, 1945).

d. Transmission of the milk factor may be obtained not only by the milk, but by inocula of living tissues (spleen, thymus, mamma, but not liver) or whole blood. In spite of its wide distribution, this factor appears to be concerned only with the formation of tumours of the breast.

e. Both the reduced liability to breast cancer brought about by deprivation of the milk factor, and the increased liability induced by its addition, can be transmitted to subsequent generations. These very remarkable facts supply evidence that multiplication of the factor occurs during the life of the mouse which has once received it (Andervont, 1945a). Genetic factors may be concerned in the ability to transmit or propagate the milk factor (Heston, Deringer & Andervont, 1944-45).

f. Male mice which have received the milk factor and are subsequently oestrogen-treated develop breast cancer (Bonser, 1944). The Strong A strain seems to be especially refractory in this respect.

Before the discovery of the milk factor it had been established that oestrogenic stimulation was concerned in the genesis of mammary cancer in mice. This subject was fully reviewed by Gardner (1939).

Three Factors affecting the Incidence of Breast Cancer

The theory has thus been conceived that three factors are necessary for the genesis of breast cancer : an agent in the milk, oestrogen, and genetic constitution. Some evidence exists (Bittner, 1944) that the latter is transmitted as a single dominant factor, but it is also possible that multiple genetic factors may be concerned, one being linked

[1] [F_1 denotes the " first filial generation " produced by crossing two unlike individuals, and F_2 the " second filial generation " produced by mating two members of the F_1 generation.—Ed.]

with the gene for brown coat colour. Van Gulik & Korteweg (1940) brought evidence to show that the genetic factor might work partly through strain-difference in susceptibility of the genital organs to oestrogen. They found that the high breast-cancer strains tested had genital organs less sensitive to oestrogen than low breast-cancer strains, and thus postulated that a greater quantity of oestrogen would be produced in them in normal conditions.

The question of dosage of the various factors must also be considered. For example, Bonser, Stickland & Connal (1937) were able to induce 5 breast cancers in 32 oestrogen-treated CBA females, in which milk factor is not normally present nor do breast tumours occur spontaneously. It would seem that the heavy dosage of oestrogen used was sufficient to initiate the cancer process in the absence of milk factor. The possibility also exists that the milk factor may vary in potency in different strains. The proof of this would require the administration of milk factor from a number of high cancer strains to low cancer mice of one strain kept under controlled conditions in one laboratory. This has not so far been done.

An obviously important aspect of this question is whether similar factors are concerned in the genesis of breast cancer in species other than the mouse, and especially in man. Evidence of a familial tendency to mammary cancer based on the incidence in near relatives of both cancer and non-cancer patients, was presented by Norwegian and Dutch investigators (Waaler, 1932 ; Wassink, 1935). This has not been confirmed in England (Passey, 1942). The method of assessment of cancer deaths in the relatives of the basal patients was, however, different in England from that in Norway and Holland, and this may account for the difference in the findings.

The demonstration of the interaction of three factors in such heterogeneous material as the human race is not likely to prove an easy task. Some interesting suggestions are made by Little (1941-42) as to the type of experiment which might be undertaken. Occasionally, exceptional opportunities occur for the study of high breast-cancer rates in certain families (Handley, 1938 ; Wood & Darling, 1943). This type of information is, however, of less value than that obtained from the more laborious and difficult studies undertaken by Waaler, Wassink and Passey. It is of interest to note that in Passey's series of 600 women with breast cancer, it has not been possible to trace a family in which the mother and the grandmother have both suffered from cancer of the breast (personal communication).

In 1944, Blank published a preliminary report of an extensive survey of the literature of the biological background of cancer until the end of 1941. This author concluded that there does exist in humans a general inherited predisposition, whether of susceptibility or of refractoriness, to tumour formation, but that other factors exist, most probably inherited independently of a general disposition, which govern the localization of the disease. If general susceptibility and inherited favourable internal environment are combined in an individual, these factors may be strong enough in themselves to lead to the formation of cancer. In addition, where general susceptibility is great in an individual, even relatively slight irritation by external agents may lead to neoplasia.

Greene (1939) described two types of breast neoplasia in two family groups of rabbits and concluded " that heredity played a fundamental role both in the occurrence of the tumors and in the determination of the tumor type ".

Chemical Carcinogens

An interesting development in the study of the interaction of several factors in the genesis of breast cancer has come from the use of chemical carcinogens in place of the milk factor. Bonser (1940) and Bonser & Orr (1939) observed the development of breast adenocarcinomas at the site of subcutaneous injection of methylcholanthrene in lard in mice of low cancer strains. One strain (IF) was more susceptible than a second (CBA). Mice of both these strains develop breast cancer when given milk factor from the RIII strain. Orr showed later (1943) that the methylcholanthrene could be administered by the intranasal route, the IF strain again being more susceptible than the CBA. The effect of the carcinogen was considered to be a distant one, the possibility of absorption through the nipple being eliminated by the use of oestrogen-treated male mice, in which nipples are not present. Administration by the cutaneous and intraperitoneal routes (Orr, 1944-45) was also effective. Bonser has recently observed (unpublished observation) that 2-acetyl-amino-fluorene administered by stomach-tube to mice of the IF and CBA strains is capable of inducing breast cancer, the IF strain being more susceptible. There is thus evidence that a chemical carcinogen can replace the milk factor, but that strains vary in their response. Whether this difference is genetic in the Mendelian sense has yet to be discovered.

Cancer of Internal Organs

Thus far, the factors which have been discussed are those concerned in the genesis of a visible, easily studied, and frequent form of cancer, namely mammary cancer. More difficult to analyze are the factors concerned with cancer in internal organs, but such studies have been stimulated (*a*) by the great variety of carcinogenic agents which has become available in the last decade, and (*b*) by the development of a large number of pure lines of mice. Two methods of approach are possible : spontaneous cancer in a particular organ may be studied in different strains and experiments can be designed to alter its incidence ; or a substance with known carcinogenic properties may be tested upon a number of strains and differences in the resulting cancer incidence observed. The use of these methods has been of great value in relation to tumours of the testis, liver, lung, adrenal, bone, stomach and skin.

Frequent interstitial-cell tumours of the testis have been observed in oestrogen-treated male mice of at least four inbred strains (Bonser, 1944), whereas they occur but rarely in other strains so treated. Such tumours do not occur spontaneously in the four strains which are susceptible to oestrogen. Gardner (1943) hybridized mice of strain A (susceptible) with mice of two other non-susceptible strains, and in 61 male hybrids found three spontaneous interstitial-cell tumours of the testis in mice living to a great age. As the hybrid mice lived considerably longer than their strain A parents, it seemed possible that increased longevity might have " afforded an adequate period for the materialization of inherent tendencies that might be elicited precociously in oestrogen-treated animals ". The author postulated two influences essential for the inception of such tumours, namely, the tumoral environment maintained by oestrogen

injections, and a genetic predisposition. A further example of the effect of prolongation of life was afforded in an experiment in which mice of the RIII strain foster-nursed by CBA were treated with the oestrogen triphenylethylene (Bonser, 1944). By this means, mammary tumours (which lead to early death in non-fostered mice) were suppressed and about one-third of the RIII mice which survived 50 weeks of treatment developed interstitial-cell tumours of the testis.

Spontaneous hepatomata occur fairly frequently in mice of the CBA and C3H strains, which were derived from a common stock (Strong & Smith, 1936 ; Gorer, 1940). They occur occasionally in other strains. Not all pathologists are agreed that these lesions are true tumours, but as metastases have been described and the tumours can be transplanted (Edwards, Dalton & Andervont, 1941-42), there is good reason for regarding them as neoplasms. Males are more commonly affected than females. When mice are treated with certain chemical carcinogens, e.g. 2-amino-5-azotoluene (Shear, 1937), carbon tetrachloride (Edwards & Dalton, 1942-43) and 2-acetyl-amino-fluorene (Armstrong, Bonser & Stickland, unpublished observation), the incidence of hepatomas in nearly all the strains tested is increased but, in general, the degree of increase varies with the carcinogen rather than with the strain. In the experiment of Armstrong *et al.*, however, strain limitation was very obvious.

When tumours of the lung in mice are considered, the true nature of the lesion is much more in doubt. These tumours appear at a late age as multiple tiny nodules, usually subpleural in position. They grow slowly and in many cases are not a cause of death. They are usually regarded as being derived from alveolar or bronchiolar epithelium ; they are sharply circumscribed and do not metastasize. Even if not neoplastic, they undoubtedly occur spontaneously with great frequency in certain strains (80% in the A strain). Little & Gorer (1943) state that Lynch & Bittner agree that the susceptibility to these lesions is dominant and that it is probably determined by a single gene. Murphy & Sturm (1925) showed that if tar was applied successively to different areas of skin, a high incidence of lung tumours of this type occurred. Since then, a vast amount of work has been done, first by Lynch and later by Andervont and his co-workers, in studying the effects of many carcinogens on many strains (Andervont & Shimkin, 1940-41). Two conclusions were reached, namely, that the appearance of these lesions is a very sensitive index of carcinogenicity, and that the susceptibility of mice to induced pulmonary tumours is linked with their susceptibility to similar spontaneous tumours. Susceptibility is fairly completely dominant in most crosses, and more than one gene is concerned (Heston, 1942).

A very interesting series of spontaneous bone sarcomas was described in the NBT strain by Pybus & Miller (1938). These tumours occurred earlier and more frequently in females than in males. In recent years the incidence in both sexes has fallen considerably, from some unknown cause which is under investigation. When oestrogen was administered to mice of this strain, and the changes in the bones were compared with mice of strains with low bone-tumour incidence (Miller, Orr & Pybus, 1943), the following conclusion was made : " While it is clear that oestrinization alone does not give rise to bone sarcomata, there is reason to believe that it can act as an adjuvant agent when the determining factor or factors are present ". The latter factors would presumably be genetic.

Occasional spontaneous adrenal cortical adenomas and carcinomas have been described in mice of both sexes (Woolley & Little, 1945a), but there is so far no strain with a high incidence of these tumours. Woolley, Fekete & Little (1940) described strain differences in both sexes in the degree of adrenal cortical hyperplasia following early gonadectomy. Two strains, dba and C3H, with a high incidence of mammary carcinoma, had more extensive adrenal cortical hyperplasia and accessory sex organ development than the C57 black strain (low incidence of mammary cancer). More recently, using the extreme dilution strain (JAXce), Woolley & Little (1945b, 1945c, 1945d) have shown that gonadectomy at birth of females and males results in the development of adrenal cortical carcinomas in all the mice surviving for a sufficient period of time. Evidences of strain differences in this type of tumour will be awaited with interest.

Epithelial tumours of the alimentary canal are very rare in mice, but Stewart & Andervont (1938) found that mice of Strong's I strain all developed an adenomatous lesion of the gastric mucosa by approximately eight months of age. The neoplastic nature of the tumour is in some doubt. A further reference to cancer of the stomach is made below. Attempts to induce gastric neoplasms in mice of numerous strains by means of carcinogens injected into the stomach wall were successful (Stewart & Lorenz, 1942-43), most of the tumours arising from the glandular portion of the stomach, though a few may have arisen from the squamous portion. There was no evidence of strain limitation.

Skin Tumours

No strain of mice has yet been described in which spontaneous tumours of the skin are at all common. The application of carcinogenic agents to the skin was, however, until about fifteen years ago the chief means of inducing cancer in the laboratory. It had been noted that in any batch of heterogeneous mice so treated there was a very great difference in time of appearance of the first and last benign tumours. Bonser (1938) attempted to select lines of mice derived from parents showing the characteristics of early and late wart formation. The technical difficulties encountered in the latter attempt prevented a successful result, but a strain of mice was established (termed IF) in which skin warts resulting from the use of several carcinogenic agents appeared earlier than in any other strain tested. Contrary to expectation, the warts, although appearing earlier, took longer to become malignant. This strain has been maintained at Leeds and was retested in 1945 (unpublished observation). The characteristics of early wart formation and delayed development of malignancy have been considerably modified.

Descendants of Methylcholanthrene-treated Mice

An entirely new approach to the study of the genetic nature of cancer susceptibility has been initiated by Strong (1944-45). Wishing to imitate in experimental animals the variable genetic background of man, this author hybridized mice of the CBA, JK and N strains by means of tandem crosses and treated the descendants with methylcholanthrene for eight generations. Under these controlled experimental conditions, a great number of neoplasms was produced in mice descendant from the methylcholanthrene-treated mice but themselves untreated. In many cases the cancers were multiple. The author concludes that biological variability

(as determined by genetic determiners) is concerned in the various types of cancer found in mice and possibly also in man. A selected strain (NHO) derived from the methylcholanthrene-treated hybrids and showing a wealth of new neoplastic diseases now becomes available for further research. It is expected that one of these diseases, namely, cancer of the stomach, will be of especial value for experimental work, in view of the prevalence of this type of cancer in man.

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From the foregoing description it will be obvious that the threshold has only just been reached in the search for the factors which are concerned in the genesis of tumours in organs other than the breast. When it is remembered how complicated are the reactions of relatively homogeneous inbred animals living under controlled laboratory conditions, it will be realised how difficult the task is likely to prove of evaluating the part played by genes, hormones, diet and other extrinsic factors in the genesis of human cancer.

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MENTAL DEFECT: RECENT RESEARCHES

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The problem of recognizing and defining what constitutes mental defect in contrast to normal mentality presents few difficulties when the deviation from the normal is gross, as in cases of imbecility and idiocy. Subjects whose mental capacities lie on the borderline between normal and abnormal are very difficult to assign to one class or the other. Cases considered defective on the basis of educational standards alone, and not physically abnormal, are described as "subcultural" by Lewis (1933). Other designations, "physiological", "residual" or "aclinical", which have been used with the same connotation, serve to distinguish the low-normal variants from the "pathological" types in which mental defect is associated with definite physical disease or malformation.

The "subcultural" or "aclinical" cases, which outnumber the others in the proportion of three to one, are more or less coincident with the group termed "feeble-minded" in England and "morons" in the United States. The recognition of these cases and the ascertainment of their frequency in the general population depends upon applying standardized intelligence-tests to children. Surveys have been carried out by various observers in random populations to determine the range of intelligence. The Northumberland survey (Duff & Thomson, 1924) of 13,000 school children and the surveys of Scottish children (Scottish Council for Research in Education, 1933) are notable examples. Roberts, Norman & Griffiths (1938) tested nearly all children in one district, and thereby obtained a very accurate estimate of the

nature of the distribution of intelligence in this sample of the community.

All these surveys showed that there was no natural line of demarcation between normals and defectives. A proportion amounting to about 2% of children can be counted defective on the basis of tests administered, but only a few of these cases are actually sent to schools for special education, and less than one-twentieth are placed in institutions. The defectives selected for institutional care or training are mainly those with severe defect. Many of those with milder degrees of defect, who are segregated in this way, display also antisocial behaviour.

Institutional Surveys

One of the simplest methods of discovering the different types of diseases associated with mental retardation is to examine large numbers of institutional cases. The first large group to be intensively studied was the series of 327 defectives classified by Goddard (1914) in the United States. Representative surveys, made by Larsen (1931) on 1,000 cases and by Wildenskov (1934) in Denmark, were followed in Britain by a survey of 1,280 cases by Penrose (1938) and in the United States by a similar survey of 347 cases by Halperin (1945). In all these investigations, attempts were made to sort out the different causes by clinical examinations and enquiry into family histories.

The earlier workers tended to separate a small group of acquired, secondary or exogenous cases from the whole, and then to suppose that all the rest were due to heredity of a simple kind. Recent work, however, has shown that such simplifications do not express the facts correctly. The comparatively rare cases in which disease or injury can be shown to be the chief cause of the mental defect do not exhaust the effects of environmental influences, which may be part-causes in a very large number of instances. Moreover, although a few rare types of defect are due to single genes, usually recessive, the mode of inheritance, by means of which intelligence of the subcultural level is produced, is very complex and multifactorial.

Prenatal Environment

In recent work on the environmental causes of mental defect, much attention has been given to prenatal influences. The very early stages of development must be involved in the malformation of mongolism, a clinical entity first recognized by a London physician, Langdon Down (1866), which affects about one in every 700 births. Advanced age of the mother is undoubtedly a significant factor in the aetiology, and this has been shown by statistical enquiry. The study of twins has been, since Galton's time, a favourite means of estimating the relative importance of nature and nurture, and it has been pursued in the hope of elucidating the cause of mongolism. Ford & Frumkin (1942) made a detailed study of the finger- and palm-prints of a pair of mongol twins. The discovery by Cummins (1936) that, in such cases, the dermal ridges show typical peculiarities, which made diagnosis both of the disease and of the monozygosity of these twins easier, emphasizes the possibility of a genetical factor in the causation besides the effect of maternal age. On the other hand, morphological similarities found in monovular twins are not necessarily always due to common heredity. More significant, perhaps, are the differences. Hobbs (1941) described a remarkable pair of monovular twins, one of whom was above average intelligence and the other almost an imbecile from birth though physically well-formed. The mental defect in the abnormal twin must have been due to some adverse prenatal influence.

Attention has been directed to the importance to the foetus of maternal health by observations on children whose mothers had rubella in the first half of pregnancy.[1] The original observations, made by Gregg (1941) in Australia, have been at least partially confirmed by later enquiries (Erickson, 1944). It is important, however, to remember that mental defect associated with congenital cataract is also found as a familial disease (Sjögren, 1933). Several infective diseases which may pass from mother to foetus and cause injury to the nervous system are now known. Ironside (1940) described an interesting case of juvenile paresis in one of a pair of fraternal twins of a syphilitic mother. Mental retardation in the affected twin was present since birth; typical neurological signs developed but no stigmata were present. Besides syphilis and rubella, the rare toxoplasmosis can pass from mother to foetus, and it causes progressive and widespread destruction of nervous tissue in congenital cases (Vail, Strong & Stephenson, 1943).

Allied to these observations are studies on the effects of therapeutic pelvic irradiation given to women in the early months of pregnancy. Goldstein & Murphy (1929) first brought forward evidence that foetal malformation could result from such treatment. Maxfield (1941) described a case of microcephaly, which might have had its origin in the radiation-therapy received by the mother, and Murphy, Shirlock & Doll (1942) reported a somewhat similar case where mental defect in the child was associated with diplegia.

Clinical Types with Genetical Origin

Most cases of defect with congenital physical abnormality or progressive disease of the nervous system are of low grade and infertile. When the cause is hereditary, the simple dominant type of transmission from parent to child is thus unlikely to be observed. Recessive heredity is recognized by familial occurrence among brothers and sisters, whose parents are normal but more often consanguineous than is usual. Cases of probably recessive genetical origin can, in fact, be picked out by finding excess of parental consanguinity. First, however, the normal frequency of cousin-marriages needs to be determined. An investigation carried out in England under the auspices of the Medical Research Council and analyzed by Bell (1940) showed that the frequency of first-cousin parents among all types of hospital patients was 0·61%. Among the parents of cases who suffered from diseases treated at neurological hospitals, the frequency was about twice as high. The frequency of first-cousin parents among 1,280 institutional defectives was found (Penrose, 1938) to be 1·9%, and the corresponding figure obtained by Duff & Dingee (1941), in a Canadian survey of 2,082 defectives, was 1·1%. The excess of parental consanguinity in these large groups has been shown to be due to the inclusion of numerous rare clinical types of congenital disease which are inherited recessively.

Familial Cerebral Diplegia

Among the important types to which attention has recently been drawn, is familial cerebral diplegia, which has been studied by Bell & Carmichael (1939). On the basis of these

[1] [See Parsons (*BMB* 873) in this number.—Ed.]

observations, Haldane (1941) suggested that the recessive gene concerned might be partially sex-linked. Stewart (1942), nevertheless, pointed out that there is a great variety of conditions which can be included among cases of diplegic defect, and that some may be due to foetal malnutrition.

Microphthalmia

Microphthalmia associated with mental defect, usually of low grade, is not very uncommon. It is a condition which lends itself readily to genetic investigation because of its easy recognition. A sibship containing four affected sibs, two imbecile twin males, and a male and female of normal intelligence, was reported by Kallman, Barrera & Metzger (1940). The parents were second cousins. This recessive type of inheritance contrasts with the sex-linked type exhibited by the cases described by Roberts (1937), one case of which was examined, post mortem, by Whitnall & Norman (1940). The optic nerves, chiasma, tracts, lateral geniculate bodies and one corticovisual area were found to be grossly deformed and the eyeballs completely disorganized.

Abnormal Lipoid Metabolism

A sibship containing six cases of the recessive juvenile amaurotic idiocy was described by Jervis (1941). The age at onset of symptoms in all instances was between 5 and 6 years. Norman & Wood (1941) described a congenital form of the disease, in which the only child of unrelated parents survived but a few days after birth; the brain showed extreme microcephaly with a lipoid dyscrasia and pachygyria. Cases of the dystrophy named "gargoylism" by Ellis, Sheldon & Capon (1936) have attracted attention from many observers. Ross, Hawke & Brown (1941) gave descriptions of four cases. Jervis (1942) described a family in which the cases were somewhat atypical, and argued that the disease was closely related to amaurotic idiocy. Halperin & Curtis (1942) have shown that gargoylism is due to a single recessive gene.

Phenylpyruvic-acid Excretors

The discovery, by Følling (1934) in Norway, of the urinary excretion of phenylpyruvic acid in certain imbeciles, stimulated a large number of researches in other countries. Cases have now been reported in England, France, the United States, Switzerland and Canada. In the analysis of 47 sibships, in each of which there was at least one case, Munro (1940) confirmed that the condition was recessively inherited; in 5 of these families the parents were first cousins. Pugh (1940) showed that such patients have an abnormally high degree of creatinuria.

An interesting experiment in the treatment of some of these cases was carried out by Bates (1939), who fed them on massive doses of thiamine; he was, however, unable to report any mental improvement. In the United States, further information about the nature of the biochemical abnormality involved has been obtained by studying blood sera and tissues. Kondritzer (1940) studied the precipitation pattern of serum proteins, and found a small but significant increase in the globulin fraction as compared with the normal. Analysis of the amino-acid content of tissue-proteins by Jervis, Block, Bolling & Kanze (1940), however, did not demonstrate any differences between normals and phenylketonurics. Jervis *et al.* (1940) also clearly demonstrated phenylalanine in the blood of such patients, confirming, by a new method, the results of the Norwegian investigators, whose recent work on the subject has been summarized by Følling, Mohr & Ruud (1944).

Some Rarer Conditions

More information has been accumulating recently about a variety of rare clinical conditions associated with mental defect. Cases of hyperostosis frontalis interna continue to be discussed in the literature, though the origin of the disease is still obscure; Stewart (1941) showed that the new bone formation in the skull is not due to brain atrophy. Ferriman (1940) discussed the irregularly-dominant type of inheritance found in oxycephaly and acrocephalosyndactyly. Both diseases, which are significantly associated with mental defect, are often sporadic in occurrence, especially acrocephalosyndactyly.

Mental defect associated with cutaneous naevi may occasionally appear in more than one member of the same family. A sporadic case was recently described by Ironside & Hill (1941). Multiple angiomata affecting the retina and cerebellum (Lindau-von Hippel disease) in 4 patients, one of whom had an affected parent, were described by Craig, Wagner & Kernohan (1941). Here, some cases may be due to new mutation.

Disagreeing with the views of some investigators who have considered myotonia atrophica to be inherited as a simple dominant character, Maas (1937) and Maas & Paterson (1943) pointed out that there is a large variation in degrees of severity in affected members of the same pedigree. This disease is evidently commoner than is usually supposed. The writers inferred, from analysis of material which covered 94 families, that the worst-affected cases appear in the latter part of the sibship, and they maintained the viewpoint, now somewhat discredited but still held by Ravin & Waring (1939), that the disease tends to become earlier in onset in each succeeding generation.

Unequivocal evidence of sex-linked inheritance in mental defect has not often been obtained. A type of severe mental defect associated with no outstanding physical abnormalities and believed to be due to a sex-linked gene was described by Martin & Bell (1943). A more convincing pedigree investigated by Allen, Herndon & Dudley (1944) showed a type of defect associated with muscular dystrophy to be confined to males and to be transmitted, for five generations, always through normal females.

Erythroblastosis Foetalis[2]

A new pathway in the investigation of the genetical causes of mental defect was opened when it was ascertained that erythroblastosis foetalis, which was already known to be the forerunner of mental defect in rare cases, was primarily due to antigenic incompatibility of the foetus with the mother with respect to one of the "Rhesus" antigens (Levine, 1942). Survivors of severe erythroblastosis are occasionally defective (Race, Taylor, Capell & McFarlane, 1943) and surveys have been carried out to discover whether antigenic incompatibility can be held responsible for defects of hitherto unknown aetiology. In spite of the suggestive results obtained by Yannet & Lieberman (1944), subsequent investigations have tended to show that Rh incompatibility is not a frequent cause of mental defect. Other antigens may, however, also be significant.

Psychological and Vocational Aspects

The hope of improving the mental capacities of defectives by subjecting them to special treatments or courses of training has been recently revived by some work in the United

[2] [See also Race (*BMB* 872) in this number.—ED.]

States. Cutler, Little & Strauss (1940) studied the effect of benzedrine administration over long and short periods on the test-scores of a group of mentally-retarded children. Immediately after administration of the drug, improved scores were obtained on the Knox Cube form boards and the Porteous Mazes. No permanent benefit, however, was derived even in patients whose treatments were continued for six months. A somewhat more optimistic view was taken by Moskowitz (1941), who believed that, in selected cases, benzedrine raised the ability to a point where educational training could be facilitated. Kephart (1939) believed that, by specific training programmes, the intelligence levels of borderline and high-grade feeble-minded subjects can be raised; his results, which were based on re-test data, were striking, but seem to require confirmation in view of the demonstrable effects of practice on test-performance (McIntosh, 1944). If re-testing is carried out at long intervals, such as 10 years, these objections do not apply, and it is interesting to note that, in a study of 85 institutional epileptic patients re-tested at intervals varying from 9 to 14 years, at a Canadian hospital, no evidence of mental deterioration was found except in three psychotic cases (Falk, Penrose & Clark, 1945).

Mental deficiency has presented some special problems in consequence of the war. An investigation, among British Army personnel, of the relationship between skin diseases and mental capacity was made by Hodgson (1941). Here, subnormal intelligence, as judged by the Matrix tests, was found prevalent in all groups referred for skin conditions, especially infestation (scabies and pediculosis) and venereal disease. On the whole, later observations (Rollin, 1943) confirmed these findings.

Much work has been done on the mental abilities of cases referred by the armed forces because of psychiatric or behaviour problems, but no great proportion of such cases has usually been found defective. Sutherland (1941) reported that the mean mental age in 45 cases of war neurosis was 12 years on the Matrix tests and 14 years on the Binet scale. Anderson (1940) pointed out that defectives may sometimes make more satisfactory naval ratings than their more intelligent brethren, provided that no psychopathic features are present.

The general principle, however, in most services has been to exclude defectives at the outset, as likely to give unsatisfactory service. Esher (1941) considered all cases below a mental age of 7 years and 11 months, which corresponds to an intelligence-quotient of 50 to 60, untrainable. In a sample of 100 cases specially studied, referred by the British Army, he found that 80% had relatively high mental ages, i.e. from 9 to 11 years. Esher made a correction for a decline in intelligence-test scores with advancing age, and further recommended that, in considering school records, careful attention should be paid to the fact that the criteria of promotion vary in different schools. The use of the Kent Test for screening purposes has been widespread because of its convenience and brevity; Rudolf (1941) examined the performances of 367 adult defectives, and showed that male responses differed somewhat from female responses, using Earl's adaptation. It is evident that, although the standards of intelligence required for success in the armed services and success in civilian life are not exactly the same, the experience in the use of tests during the war will have important future bearings upon the concept of mental deficiency in civilian life.

It must not be inferred, moreover, that the mentally defective could not adapt themselves to wartime strains. Benjacar (1940) reported that institutional cases co-operated well in civilian defence work and useful constructional tasks. They showed no more liability to panic than normals, and were very susceptible to efficient leadership; their reactions to war varied from blissful ignorance to moderately intelligent patriotic interest.

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History, Bibliography and Comment

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Paul Bert's La Pression Barométrique

" It can be said of Paul Bert as it has of Vesalius, Harvey and Boyle, that the full significance of his work could not be fully appreciated until long after his death ; but it is tragic that the chaos of a far-flung war was required to bring Bert's work into its full meaning and perspective. At a time when altitude physiologists and flight surgeons are being feverishly trained by all countries at war, it becomes of first importance to English-speaking peoples that the great classic of altitude physiology should be made available in the English language."

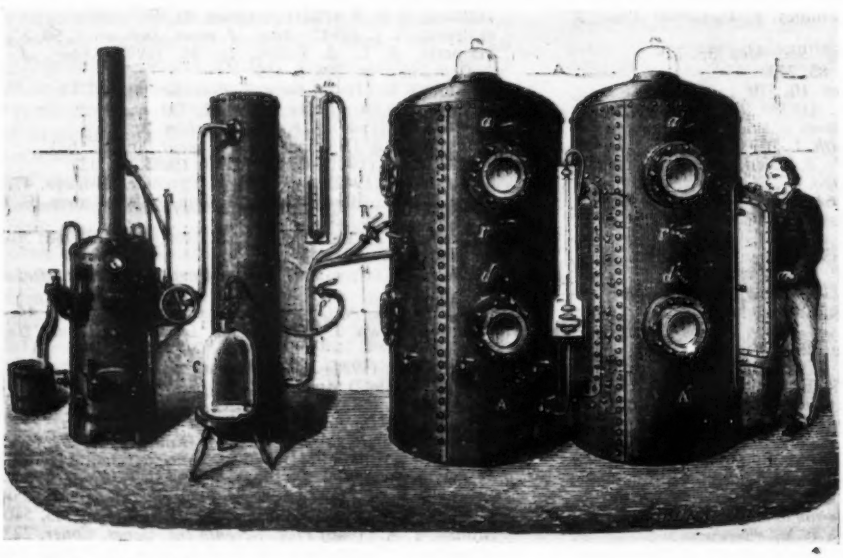
These are the opening sentences of the foreword by Professor John F. Fulton to the English translation[2], published in 1943, of Paul Bert's *La pression barométrique : recherches de physiologie expérimentale* (Paris, 1878). Professor Fulton is distinguished both as a physiologist and as an expert in medical history and bibliography, and it is therefore with special authority that he describes Bert's monumental book as " the very corner-stone of modern altitude physiology ". Perhaps greater than any verbal tribute, however authoritative, is the fact that a physiological work published in 1878 should be of sufficient contemporary scientific value to be re-published in translation in 1943. For it was not because of its mere historic interest that the recent translation was published, but because the work contains a body of detailed information and discussion that is not available elsewhere. The author of a modern work[1] on aviation medicine has written :

" Unfortunately this valuable work has been almost entirely overlooked and forgotten in our present day, yet one who aspires to a knowledge of aviation medicine must not feel that he has been successful until ' La Pression Barométrique ' has been carefully read and absorbed."

And again :

" . . . a great part of our so-called modern research in this field is nothing more than a repetition of his findings of more than 60 years ago."

FIG. 1. PAUL BERT'S APPARATUS FOR STUDYING THE EFFECTS OF REDUCED PRESSURES



Press. barom. Fig. 27, p. 631)

In these decompression chambers, Bert exposed animals, and himself, to reduced pressures. It was also in this apparatus that Crocé-Spinelli and Sivel tested their reactions to a reduced pressure equivalent to an altitude of 7,300 m., just over a year before their fatal ascent in the Zénith. The cylinders A, A′ are of riveted sheet iron, and are provided with glass portholes. In the narrow cylinder, a very low pressure (50 mm.) could be attained. By throwing this cylinder into communication with the larger cylinders, an instantaneous reduction of pressure could be effected in the latter. In front of the narrow cylinder is a bell-jar, used for experiments on small animals. In the larger cylinders, thermometers are inserted at *a*, *a′*, and cocks for taking air-samples at *r*, *r′*; *d*, *d′*; and *s*. *s′*. Manometers are shown at *m*, *m′*. At the extreme left, a steam engine which operated the pump is seen. Bert later replaced this with a gas engine.

FIG. 2. THE FATAL ASCENT OF THE *ZÉNITH*

The early afternoon of 15 April 1875. Tissandier (centre), who some years previously (1870) had escaped by balloon to the provinces during the siege of Paris, is tapping a barometer and taking a reading in response to an inquiry from Sivel (left). He tells Sivel that the reading is 300 mm. (about 7,450 m. altitude), and Sivel suggests discarding more ballast. The others agree, and Sivel cuts the release-cords of 3 sandbags. The balloon rises rapidly. Crocé-Spinelli is seen on the right, about to breathe oxygen from a wash-bottle. The 3 striped bags are of greased goldbeater's skin, and contain an oxygen-air mixture. Because of the disagreeable smell of the bags, the gas was inhaled through wash-bottles containing water flavoured with benzoin. According to Tissandier, the illustration above is an accurate representation of the scene. After Sivel had cut the release-cords, he and Crocé-Spinelli sat motionless in the nacelle. Tissandier lost consciousness at 8,000 m. About ½ hour later, he awoke for a moment and found that Crocé-Spinelli had also regained consciousness and was discarding more ballast. About 1½ hours later, Tissandier again awoke and found that the balloon was descending rapidly. Half-an-hour later, and 4½ hours after the commencement of the flight, the balloon landed and Tissandier found that his two companions were dead.

Press. barom. Fig. 86, p. 1065)

Lest it be thought that it is only since the recent war that Bert has been " discovered ", it should be added that Haldane's *Respiration*[2], the standard English-language work, accorded him full recognition in the following words :

" . . . the foundations of our scientific knowledge of the physiological effects of low atmospheric pressures were laid broad and firm by the investigations of Paul Bert, which were collected together in this book, already so often referred to, ' La Pression Barométrique ' . . . "

" . . . Paul Bert's conclusions remain valid up to the present day . . . "

La pression barométrique contains viii + 1,163 pages and 89 figures, and is divided into three parts : (i) Historical (522 pp.), (ii) Experiments (418 pp.), (iii) Recent Facts, Summary and Conclusions (115 pp) ; there are also two short appendices, a list of figures, and a table of contents. One of the outstanding impressions created by the book is its comprehensive thoroughness. In the remarkable historical part, the author has found and collated references to every aspect of his subject. In his preface he points out that he has exercised in his historical researches " les soins les plus minutieux ", and that his object has been to bring together everything that has been written on his subject. In his bibliographical researches, he tells us, he has learnt how often a summary or translation may convert the affirmations of an author to negations. For this reason he has chosen to report the exact words of the authors cited. (As if in ironic confirmation of Bert's mistrust of second-hand sources, " words " is misprinted as " works " in the English translation of this passage.)

The historical part is divided into two main sections : (i) Diminished pressure, and (ii) Increased pressure. Section (i) opens with a short survey of the lofty regions of the globe and then proceeds (Chapter I) to an enumeration of the effects of high altitudes reported by mountain travellers. The first region considered is South America, and the reports range from those of the Spanish Conquerors to those of Bert's contemporaries, including the Englishman Clements Markham. There follow the accounts of travellers to Central and North America ;

Mount Etna ; Teneriffe ; the Alps ; the Pyrenees ; the Caucasus, Armenia and Persia ; Central Asia ; Africa ; and the volcanoes of the Pacific. Chapter II is a fascinating account of balloon ascents, from the invention of the gas-balloon (the Montgolfier hot-air balloons are not included, as they did not attain significant altitudes). In Chapter III are considered relevant theories and experiments, down to Bert's own time, and Chapter IV is devoted to a summary and criticisms of observations and theories previously related.

The second section of the historical part—Increased Pressures—is also divided into four chapters, as follows : Chapter I is an extraordinarily interesting survey of the development of diving-bells and the diving-suit ; Chapter II is an account of observations made by other writers on the effects of the moderately-increased pressures which physicians were using in Bert's time for therapeutic purposes.

The title of this chapter in the original is *Faibles pressions*. In the English translation, this is rendered as " Low pressures ", whereas Bert defines *faibles pressions* as including pressures of 1-5 atmospheres. (It must be conceded that exception can also be taken to Bert's term.) Chapter III is a review of earlier experiments on and explanations of the effects of compressed air on living organisms, and Chapter IV is devoted to a Summary and Criticisms.

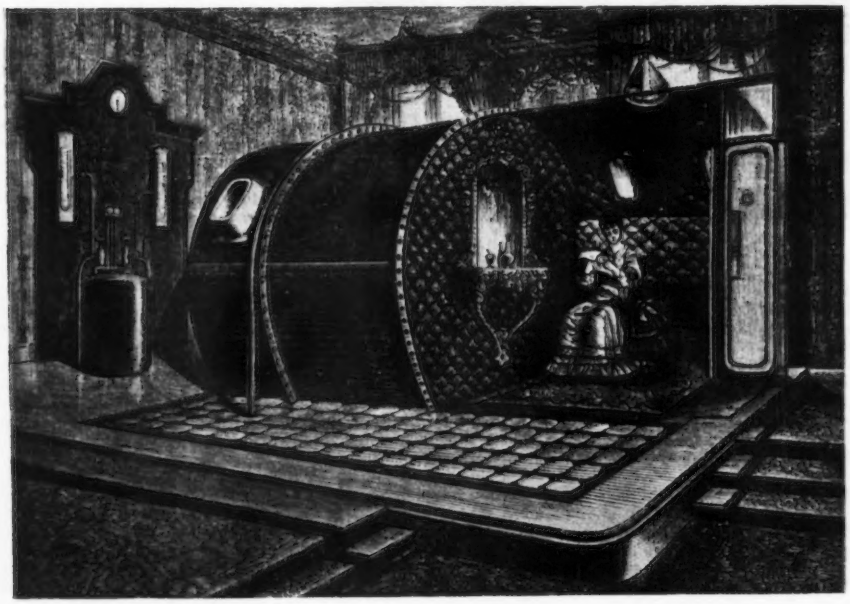
In the second part of the work, Bert describes in detail a comprehensive range of personal experiments on the effects of reduced, increased, and suddenly-changed pressures on various animals (including man), and also the effects of pressure-changes on plants, on putrefaction, fermentation, ripening of fruits, and on the " viruses " of vaccinia, glanders and anthrax. Davaine's work on anthrax had brought to Bert's notice the existence of small organisms—" bactéridies "—in the blood of affected sheep, and Bert put to the test Davaine's theory that these organisms (*B. anthracis*) were the virulent agent of the disease. He submitted samples of infected blood to oxygen at high pressures, and found that it still retained its virulence for animals. On the incorrect assumption that the organisms must have been killed by the treatment administered to them, Bert asserts that they could not have transmitted the disease, although he limits his assertion to the particular samples of blood upon which the experiments were performed. History has proved Bert wrong on this small point, but he had what seemed to be a sound basis for his incorrect assumption[4], and the outstanding characteristic of his work as a whole is that so much remains unchallenged and unsurpassed.

It is in the third part of his work that Bert includes, largely in the words of Tissandier, the sole survivor, the story of the disastrous ascent of the balloon *Zénith*, in which two of the crew of three—Crocé-Spinelli and Sivel—lost their lives from anoxia. A recent writer[5] does less than justice to Bert in saying that he *initiated* his researches on anoxia " after the disaster in 1875 to the balloon *Zénith*." By this date his work had reached an advanced stage, and had been reported in a series of communications to the Académie des Sciences of Paris and in a preliminary monograph (1874).

On 9 March 1874, Crocé-Spinelli and Sivel, intending to challenge previous claims for altitudes attained by balloon-ascent, called upon Bert and observed their own reactions to decompression in his " cloches à dépression ". In this experiment the pressure was reduced to 304 mm. Hg—equivalent to an altitude of 7,300 m. Both the balloonists experienced the disagreeable effects of atmospheric rarefaction, and both noted the favourable effects of the inhalation of oxygen from a rubber bag. In a subsequent experiment (30 March 1874), Bert was able to maintain himself in reasonable comfort, by continuous inhalation of oxygen, at a pressure equivalent to an altitude of 8,800 m. The maximum altitude reached by the *Zénith* during its disastrous flight was 8,600 m. Ten days after their test in Bert's decompression chamber, Crocé-Spinelli and Sivel made their first high-altitude flight in the balloon *Étoile Polaire*, attaining a height of 7,300 m. They both found it necessary to inhale a mixture of oxygen and nitrogen, with which Bert had furnished them.

The fatal ascent in the *Zénith* was made on 15 April 1875, this

FIG. 3. A PRECURSOR OF THE EXPERIMENTAL DECOMPRESSION CHAMBER: FORLANINI'S "AEROTHERAPEUTIC ESTABLISHMENT"



Undiscriminating and empirically-based therapeutic measures are often the precursors of new fields of scientific inquiry. The " pneumatic medicine " of the late eighteenth century, involving the inhalation of newly-discovered gases, was succeeded after an interval by inhalation anaesthesia. In 1819, Gondret, a French physician, suggested that disease might be treated by the production of varying barometric pressures in a pneumatic chamber. In 1835, another French physician, Junod, constructed such a chamber for therapeutic purposes, and similar chambers were later utilized by physicians of many countries. The illustration of Forlanini's aerotherapeutic chamber is taken from *La pression barométrique* (p. 429). In 1892, Forlanini introduced artificial pneumothorax in the treatment of pulmonary tuberculosis. A sequence of ideas may be observed here: first, the subjection of the whole patient to varying pressures; second, the variation of the barometric pressure within the pleural cavity.

(*Press. barom.* Fig. 9, p. 429)

time with a third member of the party—Gaston Tissandier—who was the only one to return alive. Bert, who was at this time away from Paris, received a letter from Crocé-Spinelli telling him of the projected ascent and of the amount of oxygen that was to be taken. Bert replied that far more oxygen than was proposed would be required, but the letter would seem to have arrived too late. The balloonists did not, in fact, exhaust even the limited supply of oxygen that they had taken with them, for when they attempted to reach for the life-giving tubes they were powerless to move their arms.

The statement[5] that Bert "built the first decompression chamber, in which low-pressure air conditions could be studied on the ground" is also misleading, as may be ascertained by a study of Bert's own book. In 1835, a French physician, Junod, who had made observations of the effects of high altitudes in several mountainous regions, constructed a spherical copper chamber, 1·3 m. in diameter, in which he studied the effects of moderate decompression in man. Junod's chamber was designed to serve therapeutic ends, and other French physicians contemporaneously engaged in similar essays in "aerotherapy". In Bert's time, such apparatuses were to be found in many European countries, and an "aerotherapeutic establishment" had been installed by Forlanini in Milan.

In his foreword to the English edition of *La pression barométrique*, Professor Fulton includes some biographical particulars of Bert. He was born in 1833 and originally chose for his profession engineering, which he abandoned in favour of law. Changing his mind again, Bert took up the study of medicine, and graduated at the late age of 30. He was an ardent Republican and anti-Clerical, and in 1881 he was made Minister of Public Instruction in the administration of Gambetta, who, it may be recalled, had escaped by balloon from Paris in 1870 during its siege by the Germans. In 1886, Bert went as Resident-General to Tongking in French Indo-China, where he died of dysentery a few months after his arrival, at the age of 53. It is noteworthy that the great body of work incorporated in *La pression barométrique* was carried out within the short space of 8 years (1869-1877).

The translation of the English edition is the skilful joint work of a linguist, M. A. Hitchcock, and her physiologist husband, F. A. Hitchcock, and they are to be felicitated upon the completion of a labour which must have been extremely arduous, but which has been well worth doing.

Finally, is not the moment most opportune for a biography of Paul Bert? There could hardly be a more fitting subject, and we are tempted to wonder whether Professor J. M. D. Olmsted, who has already given us splendid biographies of François Magendie and Claude Bernard, might not consider the preparation of a study of the life and work of the third of this great line of French physiologists.

N. H. J.

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TERCENTENARY OF THE BIRTH OF JAMES YONGE SURGEON, 1646-1721

"How many prodigious things are there done in this last age, that to the former seemed impossible?" This might well be a question asked concerning the medical advances of recent years, but it was actually written by James Yonge (1682), the first to describe the flap operation for amputation, the tercentenary of whose birth falls this year. He was born in 1646 at Plymouth, Devon, the son of John Yonge, surgeon, and his wife Joanna. By the time he was nine years old James could read and write, and in 1654 he entered the local grammar school. His stay there was short, for at eleven years of age he was at sea as apprentice to Silvester Richmond, surgeon of the "Constant Warwick", a naval vessel of 31 guns, manned by 150 men and commanded by Captain Robert Voysey. This ship acquitted herself well in action and on one occasion the surgeon's apprentice was nearly washed into the sea during a storm, but perhaps the most notable incident during his service aboard was a brush with pirates. The "Constant Warwick" had been ten days off Land's End when she sighted two ships. It appeared that the larger vessel was from Hamburg and that the crew of the smaller craft was plundering her. The pirate craft ran inshore in an attempt to lure the "Constant Warwick" aground in the shallows, but the warship gave chase, fired her guns, and captured the pirate ship within sight of many people who had gathered on the shore to witness the fight (Anon. 1849).

Samuel Pepys, the famous English diarist, records that he visited, in May 1661, a "fine ship" called the "Montagu" (Power, 1931-32), and it was about this time that James Yonge was appointed "chirurgeon's assistant" aboard her. It was in the "Montagu", in 1662, that he took part in the bombardment of Algiers. The fighting lasted six hours and the "Montagu" lost her boatswain and another man, while four men were wounded, one of whom subsequently died. Yonge recorded in his journal (Anon. 1849; Munk, 1878) that he dressed the wounded and placed them on heaps of clothes for greater comfort. He also made their barley-water, boiled gruel, prepared fomentations and poultices, and performed many other duties, including shaving and trimming, for the surgeon was not yet separated from the barber. Later in the year James Yonge returned to England, spending four months with a surgeon-apothecary at Wapping before going to Plymouth to work for his father. But his relations with his parent were not very amicable and in February 1663 he was bound for Newfoundland as surgeon to the "Reformation", a small ship of a hundred tons. On his return he sailed in the following year in the "Bonaventure" to the West African Coast, and it was during a subsequent voyage in this vessel that he was captured on 21 December 1665 by the Dutch. Imprisonment in Holland followed until he was "exchanged" early in 1667. He voyaged again to Newfoundland, but after fourteen years of naval service he resolved to settle in his native town. "I hope it will be more quiet and less dangerous", he wrote in his journal (Anon. 1849).

In 1670, while only in his twenty-fifth year, but with a wealth of experience that would have sufficed most men for a lifetime, he started to practise in Plymouth. Cases soon came. A man fell from the topmast of a ship and fractured his skull from crown to ear. He recovered under Yonge's care, and despite the jealousy of colleagues, the new surgeon prospered. As the result of his marriage about this time to Jane Crampphorne, whose family had influential connections, he was recommended as surgeon to the naval hospital. He was appointed, but this was a circumstance that nearly cost him his life, and posterity some interesting medical literature, as he almost died of spotted fever caught from his patients. In 1674, he became Surgeon-General of the Navy's deputy at Plymouth and his worldly success was assured.

It was about this time that he began to write and achieve a more than local reputation, for in 1667 he sent an account to the Royal Society of Antony Williamson, who had a bullet in

his trachea for three years (Moore, 1900). His most important work, which contains the first description of the flap operation for amputation, was published in 1679 in circumstances that were almost accidental. He visited London with the Member of Parliament for Plymouth, a Mr. Sparke, in 1678, where, " in an accidental congress of some chirurgeons " (Yonge, 1679), conversation turned on methods of arresting haemorrhage. " I quietly allowed each to give his opinion ", writes Yonge (Anon. 1849), " when I demanded if they knew a thing that could incomparably stop hemorrhage of a wound, . . . secondly, if they could cure amputated stumps by consolidation. They confessed their ignorance, and laughed at the second as impossible ; but I so explained and discovered myself, that they were extremely satisfyed, and Mr. Pearse gave me great thanks, and asked me to write more on it. So I wrote my ' Currus Triumphalis Terebintho ' . . . ". The description of the flap operation is appended to this work on turpentine.

In 1682, he published " Wounds of the brain proved curable, . . . the remarkable history of a child four years old cured of two very large depressions, with the loss of a great part of the skull, . . . ". He describes a case he attended and quotes over sixty authorities to support his thesis that wounds of the brain are not mortal. He wrote several other works during the last thirty years of the seventeenth century, but the two books described were his most important contributions to the literature of British surgery.

On 23 May 1702, Yonge was admitted an Extra-Licentiate of the Royal College of Physicians of London (Munk, 1878). At his examination he was asked " what difference was between a Gangren and a Sphacelus ", to which he replied " one was sideration of all the parts not curable but by amputation, the other of the fleshy parts and otherwise to be cured ". He was then asked " the method of curing Gangren without amputation", to which he gave a satisfactory answer. " When I received their Licence ", Yonge writes, " they all complimented me and made me sit down among them, . . . We sat 2 hours drinking good ale and clarrett, and talking sometimes of news and sometimes of art ". (Moore, 1899). Later in the year, on 3 November, Yonge was elected a Fellow of the Royal Society.

James Yonge was now a person of consequence in his native town. In 1694, he had been Mayor of Plymouth, and it is interesting to note that in 1703 his patients numbered 444, of whom 14 died (Anon. 1849). From this time onwards he lived in semi-retirement, but his last recorded duty was his most famous. Sir Cloudesley Shovell, commander of the English fleet, was returning to England in " The Association " when his flagship was wrecked on the Bishop Rock near the Scilly Isles. All the crew perished, the half-drowned admiral dying after being washed ashore. His body, originally buried in the sand, was exhumed and brought to the citadel at Plymouth, where it was embalmed by James Yonge. Thus he finished his professional career and in the seventy-sixth year of his age, on 25 July 1721 (Munk, 1878), James Yonge died and was buried in the church where he had been baptized, namely, St. Andrew's, Plymouth.

F. Tubbs

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LEIDEN AND EDINBURGH :

A MEDICAL PARTNERSHIP

The geographical progress of medical education is one of the most remarkable phenomena in the history of medicine. Scientific medicine, as opposed to magical healing, had its birthplace in Greece. From Greece, it passed to Rome and Alexandria, then by way of the Moslem Empire to Salerno, the first great medical school of Europe. Salerno yielded precedence to Bologna and Montpellier, and eventually Padua became recognized as the leading medical centre. At the Reformation the restrictions imposed upon Padua and other Catholic Universities provided an opportunity for the newly established university of Leiden (Leyden), which was open to all, irrespective of religion.

From the date of its inception in 1575, Leiden University had a Faculty of Medicine. There was a galaxy of distinguished anatomists, commencing with Peter Paaw, one of the founders of the school, and including Ruysch, who invented a method of injecting blood-vessels, Tulp, who was depicted by Rembrandt in " The Teacher of Anatomy " and who was the first to describe the East Indian disease beri-beri, and Bidloo, who wrote a textbook of anatomy, beautifully illustrated by himself. Another early teacher at Leiden was Francis de la Boë (Sylvius), equally distinguished as an anatomist and as an exponent of clinical medicine, one of the first to teach clinically, by the bedside.

The Leiden School, with its brilliant staff, attracted students from all countries. As the teaching was in Latin it was intelligible to any person of education. From England, Scotland, Ireland, and even America, students came to Leiden in increasing numbers. Sir Thomas Browne graduated M.D. there in 1633, and from Scotland came a noteworthy trio, Sir Robert Sibbald, Dr. James Halket, and Dr. Archibald Pitcairne, who were appointed, jointly, in 1685, to the chair of Medicine in the Town's College, which later became the University of Edinburgh. Archibald Pitcairne, the youngest of the three, who attained distinction for championing Harvey's discovery of the circulation of the blood, was appointed to the Chair of Medicine at Leiden, where he numbered among his pupils Herman Boerhaave and Richard Mead. Mead became the leading London physician of his day, and Boerhaave, who succeeded Pitcairne, rose to be the most famous of all the Leiden teachers and one of the greatest physicians of all time.

Another of Pitcairne's students was John Monro, a surgeon in the Army of William of Orange, whose son, Alexander Monro (primus), must share with Pitcairne the credit of founding the Medical School of Edinburgh. John Monro envisaged a school for Edinburgh on the pattern which had proved so successful at Leiden, and he trained his son Alexander to be the first professor of anatomy and the first of a dynasty of three Alexander Monros who held the Chair for 128 years. The first Alexander was a pupil of Boerhaave, and so was Sir John Pringle, the founder of modern military medicine.

After the death of Boerhaave in 1738, Scottish students continued to frequent Leiden for many years. Among them were four of the great family of Gregory, which produced no fewer than sixteen professors within a few generations. One of the four was James Gregory, whose name is still associated with " Gregory's powder ", and who succeeded his father as professor of medicine in Edinburgh.

Thus did Leiden contribute in large measure to the foundation of the Edinburgh Medical School, and thus further links were added to the chain which had originally been forged so well by Archibald Pitcairne.

Douglas Guthrie

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TWO MEDICAL TRUANTS[1]

The study of medicine is long, arduous, and expensive. Is it strange, therefore, if some medical men, having spent their precious youth preparing themselves for a medical career and having lived casually for a while with their lawful wedded wife, the muse of medicine, should suddenly be led astray by the siren call of other muses, henceforth to live a life of adultery with one of these? Some are forced into medicine to humour a paternal whim. Their profession soon becomes distasteful to them, so that they play the part of truant gladly. Others, undecided and vacillating in mind, half-heartedly embark upon a medical career, which after a time ceases to allure them, when they drift into some other pursuit. A few deliberately take up the study of medicine, which they intend never to practise, realizing the advantages of its scientific training as a preparation for other callings.

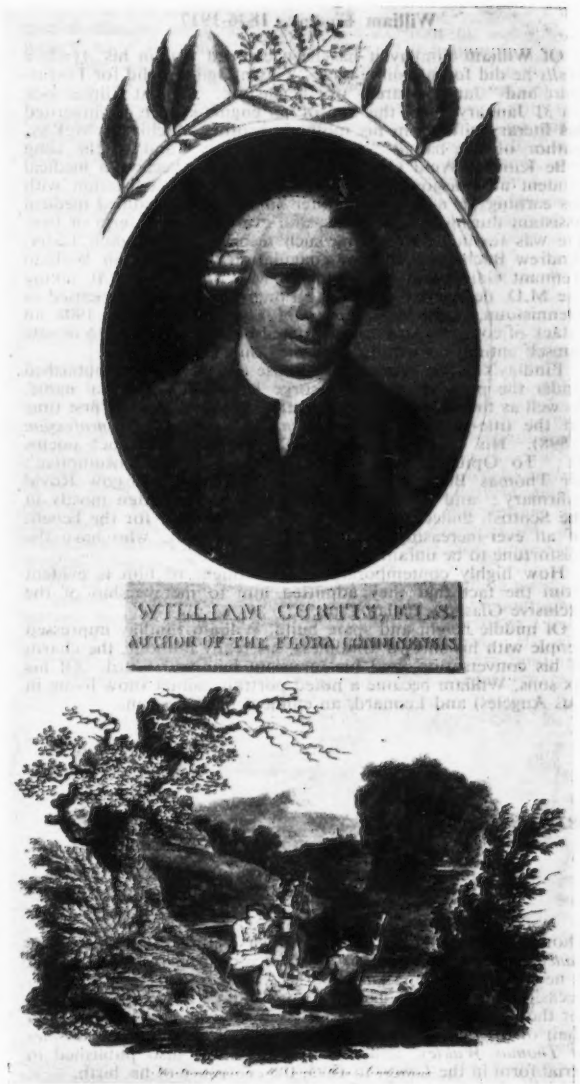
Impressive in its length, variety, and distinction is the list of physicians and surgeons who turned to literature, art, politics, sport, or murder for a vocation, a profession, a means of livelihood, or a hobby. Of those who fell enamoured of the muse of literature some continued to practise their art, writing in their spare time only, while others forsook medicine almost as soon as they had qualified.

It so happens that two truants appeal to the commemorative mind this year: William Curtis, who deserted medicine to become one of England's most distinguished botanists, and William Findlay, who in his hours of leisure and in his enforced retirement, strayed into the pleasant fields of literature.

William Curtis, 1746-1799

Already as a boy Curtis showed his love for natural history by spending his pocket-money on botanical books. One of his greatest friends was Thomas Legg, ostler at the Crown Inn, Alton, a learned botanist, in whose company he would roam the countryside. "Such an intimacy for their son sober parents might have deprecated, and ambitious ones have contemned; yet hence the youthful Curtis imbibed that taste for natural knowledge, which proved the source of his future fame and profit, and above all, of what is not always justly appreciated, his happiness" (Abraham Rees: Cyclopaedia, 1819, x.).

Born at Alton on 11 January 1746, the son of a tanner, at the age of 14 Curtis was apprenticed to his grandfather, a local surgeon-apothecary. Six years later he went to London to finish his medical education, becoming associated with a Mr. Talwin, of 51, Gracechurch Street, whom he succeeded in business. "The apothecary was soon swallowed up in the botanist, and the shop exchanged for a garden." In 1771, Curtis sold his practice and bought an acre of land in Bermondsey, where he planted a botanical garden for his students; for, in addition to his medical practice, he was demonstrator of practical botany at the medical schools. The following year he was appointed demonstrator of plants and *praefectus horti* to the Society of Apothecaries. In 1779, he acquired a more extensive garden at Lambeth Marsh, which, 10 years later, the smoke of London spoiling his plants, he moved to a site now occupied by the Brompton Hospital. His first published work was a pamphlet, *Instructions for collecting and preserving insects* (1771). The first number of *Flora Londinensis* was issued in May 1775, and that of the *Botanical Magazine* (still published and edited at Kew on behalf of the Royal Horticultural Society) in February 1787, the former, in his own words, bringing him praise and the latter bringing him pudding.



A original Fellow of the Linnean Society (his is the third signature of the Roll Book), Curtis stimulated in his fellow-countrymen a popular taste for botany and horticulture. He was an entertaining companion, an accurate observer, a hard worker, but a poor business man.

Afflicted with a "disease in the chest, supposed to be of a dropsical nature, but which was rather, perhaps, an organic affection of the heart", he died at Brompton on 7 July 1799, at the early age of 53.

London has two memorials to Curtis: a plaque on the wall of the building in Gracechurch Street, which occupies the site of the house where he practised as apothecary; and his tombstone in the old Battersea Parish Churchyard. Arrangements have been made to renovate the stone and to restore its inscription.

An exhibition of *Curtisiana* at the Curtis Museum, Alton, was opened on 11 January by Mr. John Gilmour, assistant director of the Royal Botanic Gardens, Kew.

[1] [An account of many other medical truants is to be found in Lord Moynihan's Linacre Lecture: *Truants: the story of some who deserted medicine yet triumphed*, Cambridge, 1936. This is an expanded version of the original lecture.—ED.]

William Findlay, 1846-1917

Of William Findlay it has been claimed that in his *Ayrshire idylls* he did for Ayrshire what " Gavin Ogilvy " did for Forfarshire and " Jan Maclaren " for Perthshire. Born at Kilmarnock on 31 January 1846, the son of an engine-keeper, he inherited his literary gifts from his mother's brother, Archibald McKay, author of the ballad " My First Bawbee " and of the song " Be Kind to Auld Grannie ". In 1866, he became a medical student at Glasgow, paying for his university education with his earnings as a carriage-painter and as an unqualified medical assistant during the vacations, and even missing a term or two. He was fortunate in having such teachers as the great Lister, Andrew Buchanan of blood-coagulation fame, and Sir William Tennant Gairdner. He graduated M.B., C.M. in 1870, taking the M.D. degree 8 years later. For many years he practised in Dennistoun, a growing suburb of Glasgow, until in 1906 an attack of coronary thrombosis forced him to retire and to devote himself entirely to writing. He died on 11 May, 1917.

Findlay's earlier works, both prose and verse, were published under the pseudonym of " George Umber ". The real name, as well as the pen-name of the author appeared for the first time on the title-page of *Robert Burns and the medical profession* (1898). His *Carmina medici* (1902), which include such poems as: To Opium; The Hypochondriac; The Consumptive; Sir Thomas Browne; Sir W. T. Gairdner; Glasgow Royal Infirmary; and Therapeutics o' Gowf, were written mostly in the Scottish dialect, a glossary being provided " for the benefit of an ever-increasing number, I grieve to say, who have the misfortune to be unfamiliar with that tongue ".

How highly contemporary poets thought of him is evident from the fact that they admitted him to membership of the exclusive Glasgow Ballad Club.

Of middle height and spare build, William Findlay impressed people with his shrewd kindliness, his ready humour, the charm of his conversation, and his luxuriant hair and beard. Of his six sons, William became a noted portrait painter (now living in Los Angeles) and Leonard, an eminent paediatrician.

W. R. B.

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THOMAS WAKLEY

Thomas Wakley (1795-1862), founder and first editor of the *Lancet*, the most famous of all medical journals, is the hero of a new biography by Dr. Charles Brook. It is not the first occasion on which he has been the subject of the biographers, for the late Sir Squire Sprigge, a recent occupant of the editorial chair of the *Lancet*, wrote a charming book on *The life and times of Thomas Wakley*, and his biography was also published in serial form in the *Lancet* in 1895, the centenary of his birth.

In *Battling Surgeon*, Dr. Brook paints a vivid picture of a great medical reformer who devoted his life to fighting the corruption prevalent in hospitals and medical schools a century ago. Many other notabilities of the period are included in this picture, making the book a valuable and interesting addition to the literature on medical history. In the opinion of the author, Wakley was the most important member of the medical profession in Britain during the nineteenth century, surpassing even Lister, who was " a mere pygmy by the side of Wakley ".

This book reveals the great changes which have taken place in the last hundred years, for when Wakley received his medical qualification medical practitioners were not registered nor properly trained, there was corruption among the leaders of the medical profession, dissecting rooms were still supplied by resurrectionists and murderers, the treatment of hospital patients was often deplorable, and the adulteration of foodstuffs was scandalous.

When Wakley founded the *Lancet* he began to attack these abuses. One thing which particularly incensed many of the leading medical teachers of the time was his publication of their lectures, thus making available for sixpence a time (and with much other information) lectures for which students paid five pounds a session. Attacks on Wakley followed, but he retaliated by publishing accounts of maladministration in the medical schools and malpractice in the hospital wards. This led to his involvement in much litigation, in which he was as often the loser as the winner. Much of the book is devoted to Wakley's battles in the courts and to the many other controversies in which he figured. Dr. Brook has obviously gone to a considerable amount of trouble to consult original sources for his material; this makes the book all the more valuable, for many of these sources are now difficult of access. He has produced a fascinating chapter in the history of medicine in Britain. One reads again of the " row " in 1836, when the students from Guy's Hospital were suddenly refused admission to the operating theatre at St. Thomas's (then adjacent to Guy's), a privilege previously allowed, of the burning of Wakley's house in Argyll Street by sympathisers of the Cato Street conspirators, and of Wakley's unscrupulous exposure of John Elliotson (" Dr. Goodenough " in Thackeray's *Pendennis*). Elliotson sincerely believed in the curative value of mesmerism in certain conditions, but Wakley exposed him by a trick and almost brought to an end the career of one who was a friend of Dickens and Thackeray and who was held in high esteem by orthodox members of the medical profession. Wakley's work as a coroner and a member of Parliament is also fully recounted.

Dr. Brook strives to show how the errors of the past can help to solve the problems of the future. He believes that " the age of the bottle of medicine and the smile as a doctor's sole stock-in-trade is passing, and we now look forward to the advent of a new and intelligent conception of health and disease . . . The fact remains that the family doctor is slowly but surely being squeezed out of existence. The establishment of publicly provided diagnostic, supervisory and treatment centres has deprived the family doctor of much of his former work, and the time does not seem far distant when the domiciliary midwife and maternity unit will entirely replace the hurrying and harassed doctor with his instruments all ready in his black bag."

A book of such importance as this deserves a better format and more expensive production. With so much of value between its covers, the lack of an index is a serious omission, affecting particularly the medical historian, who will assuredly consult this book. But perhaps the author, in keeping with the advanced views both of himself and Wakley, feels that his book should be produced at a price low enough to make his story available to all, and thus secure that appreciation of his hero which he feels is at present lacking. [For price and other details, see *BMB* **922.**]

L. T. Morton

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THE APOTHEOSIS OF PARACELSUS

Paracelsus: a genius amidst a troubled world, by Basilio de Telepnef, is, according to the dust-wrapper, the first step in a campaign to introduce " the true Paracelsus " to the English-reading public. It will be followed by unabridged translations of the works of Paracelsus. Basilio de Telepnef's volume is a short biographical study, published by Zollikofer of St. Gallen, and most attractively printed. The author is a member of a Paracelsus Society which was formed recently at Einsiedeln, the birthplace of Paracelsus, and his study can be recommended as providing a short (93 pp.) and easily readable study containing the essential facts of Paracelsus's life and work. In places, the style of the English translation is peculiar, but this does not constitute a serious obstacle to enjoyment.

Unfortunately, however, the author shows not the least pretence to objectivity in his treatment of his subject. His attitude is one of uncritical adulation, and he speaks, for example, of the " marvellous cures " of Paracelsus as if they were well-

attested facts. The allegation by Oporinus, Paracelsus's laboratory assistant, that Paracelsus was " perpetually drunk " is described (p. 58) as " the Basle calumny " and (p. 87) as " the crassest instance of defamation by an ungrateful disciple ", but we are not given the slightest hint of any reasons for disbelieving this allegation. It is surely not inconsistent with what we know of the violence and extremism of Paracelsus's personal character that he should often drink to excess. It is, at any rate, a little difficult to believe in him as a teetotaller, and if some passages in his writings were not composed in a state of inebriation, they must have been the product of a mental state not far removed from it. However, if one may judge from this short study by de Telepnef, the new Paracelsus Society is the organ of a Paracelsus Cult. The most obscure verbiage of Paracelsus is holy writ, to be reverently searched for prophetic anticipations of modern scientific discoveries. Dr. J. Strebel, in a short introduction, refers to Paracelsus as " this wizard " and says that " the vitamines (sic) were clearly recognised by him ". In a similar vein, de Telepnef asks :

" . . . were these clear notions of our modern ' discoveries ' but visions of an enlightened seer, or (and much in Paracelsus's writings points to this latter conclusion) did some of the medieval ' alchemists '—their secrets locked safely under the sombre vaults of dark laboratories, their dangerous ' knowledge ' inherited from the ancient ' magicians ', wisely guarded in occult circles, far aloof from the profane world—did they in fact know infinitely more than we, in our pride, deem it possible? "

This uncritical—and almost irrational—Paracelsus-worship is not a new phenomenon. In 1837, a German writer, Quitzmann, wrote of Paracelsus as " the reformer par excellence " and of Harvey, by comparison, as " the author of a secondary discovery ". Daremberg[1] appropriately commented :

" Quoi ! une découverte qui change la face de la science,une découverte qui contient en germe tous les progrès futurs de la médecine, en un mot, la vérité, la réalité ne serait pas mille fois plus importante que des idées *a priori*, qui n'ont eu d'echo que dans quelques cerveaux prédisposées aux aberrations "

It would be impolite to attribute to members of the Paracelsus Society " brains predisposed to aberrations ", but it is not too much to ask that their future publications should be inspired by a rather less mediaeval scientific outlook. To imply, as de Telepnef does in an Addendum, that passages in the writings of Paracelsus have some prophetic relation to the atomic bomb, is on a level with forecasts of the date of the Millennium derived from a study of the Old Testament or the architecture of the Great Pyramid.

N. H. J.

884

HISTORY OF A MENTAL HOSPITAL

The treatment of mental disorders (ancient and modern), by Richard Eager, commemorates the centenary of the Devon Mental Hospital, which was founded in 1845 as the Devon County Lunatic Asylum. The author of this little book was for thirty years a member of the hospital staff and its medical superintendent for fourteen, and is therefore well qualified to be its historian. The first part of the book is a brief history of the care and treatment of the insane from the earliest time. In referring to matters not strictly germane to psychiatric history, the author sometimes falls into error, as when he states that Harvey first explained the circulation of the blood in 1610 and that he died in poverty. It is generally accepted that Harvey gave the first public exposition of his views in his Lumleian Lectures in 1616, and, although his practice is said to have fallen off after the publication of his book on the circulation, he never knew poverty ; indeed, he left more than £20,000 to his brother Eliab, apart from other bequests. The book contains many misprints and it is particularly disquieting, in a history of mental disease, to come upon such distortions of well-known names as " Kraeplin ", " Esquicol ", " Sherringdon ", and " Wagner von Jaurigg ".

In the second and third parts, dealing with the history of his own hospital, with recent advances in psychiatry, and with the changing outlook on mental disease, the author is on surer ground. The story of a particular hospital, when fully told and well documented, is a source book of primary importance, and Dr. Eager could have expanded that part of the book which tells the story of the Devon Mental Hospital and of the eminent physicians who have served it, to the advantage of his present readers and of future historians of psychiatry. [For price and other details, see *BMB* **921**.]

W. J. B.

[1] Daremberg, C. *Histoire des sciences médicales*, vol. 1, p. 57, Paris, 1870

885

JOHN HUNTER

A bibliography of the works of John Hunter has recently been prepared by W. R. Le Fanu[2], librarian of the Royal College of Surgeons. The list records all editions of Hunter's works known to the compiler ; it does not deal with his contributions to periodicals nor with his case-histories and descriptions of specimens posthumously printed in the catalogues of the Hunterian Museum. The holdings of 25 of the most important medical libraries are recorded in each entry.

Mr. Le Fanu points out that, besides their outstanding position in scientific literature, Hunter's books are of bibliographic interest because several of them were published at Hunter's own house, 13 Castle Street, Leicester Square, London. He will welcome additions, corrections and records of library holdings in order that a detailed bibliography of Hunter may be prepared.

L. T. M.

886

DOMESTIC MEDICINE

Among the numerous works on household or popular medicine which have appeared since the *Regimen* of the School of Salerno first created a taste for this type of literature, none has enjoyed a wider circulation that Buchan's *Domestic Medicine*, which was first published in 1769. There have been many editions since then, and the book is in use even to this day as a family guide to health. William Buchan practised in Edinburgh and subsequently in London. There he died in 1805 and was buried in Westminster Abbey. Buchan's treatise gives an interesting picture of the times in which he lived. He states that " one half of the children born in Great Britain die under twelve years of age " and, of smallpox, he writes : " This disease is so general that few escape it at one time of life or another ".

Douglas Guthrie

887

LIBRARY OF THE WELLCOME HISTORICAL MEDICAL MUSEUM

Dr. E. Ashworth Underwood, the director of the Wellcome Historical Medical Museum, 183-193 Euston Road, London, N.W.1, asks us to announce that a catalogue of the extensive library of the museum is being prepared, but that it will be some time before this work will be published. Meanwhile, if any

[2] *John Hunter ; a list of his books.* Compiled by W. R. Le Fanu. Printed for the Royal College of Surgeons of England at the University Press, Cambridge, 1946. 31 pages.

person who is preparing a bibliography of the works of any writer in the field of medicine or the allied sciences, desires to include the location of known copies of the different works, Dr. Underwood will be please to send him on request a list of the various works and separate editions of that writer which are in the library of the Wellcome Historical Medical Museum, and applications should be made to him in writing.

It is hoped to open the library for the use of students at an early date, and an announcement will be made to that effect, but meanwhile the above particulars will be supplied on request.

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SPANISH MEDICAL BIBLIOGRAPHY

El Indice Médico Progresivo (Barcelona). This new periodical provides a monthly index of all Spanish medical literature. The first number was published in April 1945 and comprises 4 sections: (i) A numbered and alphabetically arranged list of the periodicals covered, with date of publication of the issue indexed, (ii) a contents-list for the particular issue of each periodical, numbered as in (i), (iii) an alphabetical author-index including all joint authors and (iv) a subject-index. Number 12 of Vol. 1 will include a general index to the volume as a whole.

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SWISS MEDICAL BIBLIOGRAPHY

Bibliographia Medica Helvetica, 1, 1943. This is the first volume of a new bibliography of Swiss medical publications, issued by the *Académie suisse des sciences médicales* in collaboration with the *Bibliothèque nationale suisse*. It is to appear once or twice a year and will include all the publications which have appeared in the course of a year, but it is also possible to obtain separate parts referring to a particular subject. The bibliography is arranged in classified order, according to the Universal Decimal Classification, with subject and author indexes. There is also a table of the relevant parts of the classification. This publication may be obtained from Benno Schwabe & Co., Basel, price 15 Swiss francs.

890

THE CAJAL INSTITUTE

Volume 36 (1944) of the collected works of the Instituto Cajal, *Trabajos del Instituto Cajal de Investigaciones Biológicas*, published annually under the auspices of the Consejo Superior de Investigaciones Cientificas, has recently been received. It contains the following articles: "A Sheath enveloping the entire Ramifications of the Axon in the Motor Endings of Striated Muscles," by J. F. Tello; "Contributions to biological research. Part II: Animal Movements. Migrations," by Domingo Sánchez y Sánchez; "Experimental Poliomyelitis," by J. Sanz Ibáñez; "Contribution to the Study of the Cerebellar Neuroglia of the Lamb," by Demetrio Dimoff; "New Staining Technique specially applicable to Sections of Organs of the Nervous System," by José Luis Arteta Algibez; "Contribution to the Histopathology of Human Lathyrism," by C. Oliveras de la Riva; "The Mechanism of Excitation of the Chemoreceptors and Baroreceptors of the Glossopharyngeal Nerve, by means of a Reflex Arc between the Vago-afferent and Sympathetic Systems," by F. de Castro. The first and third articles are accompanied by summaries in English and German and the last by a summary in English.

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TROPICAL SCIENCE IN SWITZERLAND

In 1944 the Federal State Council for the creation of employment approved the foundation of a Swiss Tropical Institute in Basel which was to combine scientific research with the training of medical men, missionaries, zoologists, veterinary surgeons, pharmacists, manufacturers, engineers, etc., for work in tropical and subtropical countries. A tropical clinic was opened by the Institute in the Hilfsspital in Basel, with escaped prisoners of war and internees from Mediterranean regions, suffering from a form of malaria very prevalent in tropical countries, as its first patients. The teaching activities of the Institute include (*a*) a one-year general tropical course at the University covering all matters of which a European travelling to the tropics should be at least roughly informed, but with a slightly differing syllabus for medical men; (*b*) a 3-year course for young people designed to give a thorough training for practical work in the tropics in one of three spheres, namely: as a planter, sugar chemist or trader. Diplomas are awarded for both courses. Research on a number of malarial problems has already been begun, and it is thought that, with the post-war return of Swiss and other European business people, missionaries, etc., to Switzerland, the work of the clinic and the scope of the Institute's research will expand. A comprehensive research index of tropical literature is being compiled to facilitate this work. An expedition to West Africa was planned for the latter half of 1945, to make direct personal contacts with the authorities there, to visit tropical institutes and hospitals and collect information regarding the diseases treated and the researches pursued therein, and to arrange for the possible visits of Swiss scientists for further training.

With the foundation of the Tropical Institute there came into being a new periodical, the *Acta Tropica* which, as stated in the foreword to Volume 1, is intended to be "not merely the organ of the Tropical Institute but an independent international scientific review treating of the whole sphere of tropical science." The *Acta Tropica* is edited by Professors R. Geigy, A. Gigon, F. Speiser and R. Tschudi, "in collaboration with eminent Swiss and foreign specialists," and published by Verlag für Recht und Gesellschaft AG., Basel. One volume comprising four numbers of 96 pages each is issued annually at a cost of Fr. 30 (single numbers, Fr. 9). The bound copy of Volume 1 (1944) and the first three numbers of Volume 2 (1945) which have reached us amply confirm the stated aim of the *Acta*, which is to afford scope for the presentation of "scientific research pure and simple as well as that undertaken with a view to practical application" in the fields of anthropology and ethnography, natural history of the tropics, tropical agriculture, tropical medicine, and veterinary surgery and medicine in the tropics. A random sample of the titles of original articles will illustrate this. Volume 1: The Influence of Polynesian Culture on New Caledonia and the Loyalty Islands; Tropical Medicine in the Middle East; India and the Dual Organisation; The Role of Parasitic Worms in the Tropics; The Yellow Populations of Africa; Progress in the Control of Typhus and Malaria. Volume 2: International Campaign against Foot and Mouth Disease; Plasmodium vivax and Feulgen's Nuclear Reaction; Phlebotomus in Switzerland; The Attitude of Catholic Missions to Native Art in the Tropics; The Secret Societies of West Africa; The Importance of the Medical Mission in Tropical Medicine. The articles appear in German, French or English, and are each accompanied by summaries in the other two languages. The international bilbiography included in each number is classified according to the decimal system and should prove invaluable to students of tropical science. A book review section and a number of short scientific communications and reports under the heading "Miscellanea" complete the contents of this well-produced and beautifully illustrated journal.

M. B. W.

892

ROYAL COLLEGE OF SURGEONS OF ENGLAND

General Annual Report of the Council, 1945

PUBLISHED BY THE COLLEGE, LINCOLN'S INN FIELDS, LONDON, W.C.2.
26 pages. 21.5 × 14 cm.

This report, which covers the period August 1944 to July 1945, opens with an account of the visit to the College of H.M. Queen Mary on 13 July 1945.

The death at the age of 95 of Sir Buckston Browne has deprived the College of one of its greatest benefactors. His most important donation to the College was a gift of £100,000 for the establishment and endowment of the Buckston Browne Surgical Research Farm, Downe, Kent. The death of Sir William Girling Ball is also recorded in the report.

During the year 27 fellows and 571 members were admitted by examination. In the previous report[1] there was stated the intention of the Council to seek power to institute a final examination for Fellowship of the College adapted to the needs of ophthalmological candidates. This principle has now been extended to cover the case of otolaryngology. A higher quali-

fication in dental surgery has for long been considered, and "Fellowship in Dental Surgery" has now been adopted as a suitable title.

Sir William H. Collins has donated a further £100,000 to the College, for the endowment of the department of anatomy and the institution of a chair of human and comparative anatomy. Prof. F. Wood Jones has been appointed to this professorship.

The College is to appoint from time to time research associates, with the object of providing for interested persons a suitable association with the College and its museum.

In the department of pathology much thought is being given to reconstruction plans and to methods of arrangement and display in the future museum. New specimens which have accumulated since 1941, over 600 in number, are being classified and prepared for museum purposes.

The library office returned to the College during the year, and the reading room was reopened. The return of the books from war-time evacuation is almost completed. Accessions to the library include 100 volumes bequeathed by the late Sir Humphry Rolleston.

The research work briefly noted in the report is more fully discussed in the scientific report.[2]

During the year the College has maintained its policy of securing properties adjacent to its original buildings, plans for the rebuilding of which are under consideration.

[1] [See BMB 606/101.] [2] [See BMB 893]

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ROYAL COLLEGE OF SURGEONS OF ENGLAND

Scientific Report for the Year 1944-1945

PUBLISHED BY THE COLLEGE, LINCOLN'S INN FIELDS, LONDON, W.C.2
24 pages. 24.5 x 15 cm.

Department of Pathology: The newly-appointed Sir William H. Collins professor of pathology, Dr. R. A. Willis, commenced duties in April 1945. Much preparatory work has been performed in connection with the re-establishment of the museum. The specimens surviving from the 1941 disaster, which had been dispersed in various centres, have now been returned to the College. Accessions to the museum during the year number 230.

Department of Anatomy: During the earlier part of the year the main preoccupation of the anatomical museum staff continued to be the supervision of the dispersed specimens and the reception, registration and storage of incoming material. Professor F. Wood Jones was appointed to be first occupant of the Sir William H. Collins chair of human and comparative anatomy. Anatomical research during the session has included an investigation of the oesophageal vasculature. Information on anatomical matters has been supplied to various enquirers. 104 specimens were added to the anatomical museum during the year.

Bernhard Baron Research Laboratories: The work in these laboratories during the past 5 years is summarized. Up to 1941 published work on trauma and repair showed traces of having been influenced by the investigations carried out between 1914-18. Thereafter the outlook was influenced by the mass of knowledge which accumulated on growth, metabolism and nutrition. The work in these laboratories was therefore directed to studying the mechanisms involved in the maintenance of a constant blood-volume. It was found that, after haemorrhage, protein was being added to the extra-vascular fluid entering the circulation to restore the blood-volume. The added protein came partly from the liver and partly from the muscles. Later studies showed that plasma protein moved out of the circulation as rapidly as it entered after haemorrhage. The problem of protein synthesis was attacked by indirect methods, using human patients. In a normal individual the amount of protein destroyed each day is equal to the amount synthesized. The net intake of protein can be estimated by determining the amount of protein in the food and subtracting from this the amount not absorbed in the gut. From the urinary nitrogen content the amount of protein destroyed in the body each day can be estimated. In 1943 it became possible to study in detail cases of infective hepatitis and allied hepatic diseases, thus providing data on the rate of protein synthesis. The value of methionine in the prevention of hepatic necrosis was also observed. It is widely recognized that excessive protein loss is an inevitable consequence of trauma, and is thus a phenomenon common both to hepatic disease and to injury. The necessity for the assimilation of adequate protein by patients became obvious. There followed the use of pre-digested proteins (hydrolysates), the employment of which speeded up wound-healing in patients previously showing no progress on account of grossly inadequate protein intakes.

As an outcome of various reports of the above work, the laboratories were asked to provide the nucleus of a laboratory team to study the results of the long food-deprivation suffered by the people of western Holland and to report on the most effective treatment of the starvation state. A report on this work is being submitted to the Medical Research Council.

Dr. F. K. Sanders has continued his work on peripheral nerve injuries.

Details of papers published from the department's research laboratories during the year are included in the report. (For review of previous report, see BMB **606/102.**)

894

LONDON COUNTY COUNCIL

Interim Report of the Medical Officer of Health and School Medical Officer for the Year 1944

LONDON, P. S. KING & STAPLES, LTD., 1945. 50 Pages. 1s. 6d. [£0·075]

The interim report for the year 1944 of the County of London Medical Officer of Health and School Medical Officer (Sir Allen Daley) is the most comprehensive report of the series published since 1939, and for the first time since then it quotes birth- and death-rates.

The report states that London's population was down by 40% in 1944 compared with 1938, i.e. from 4,062,800 to 2,462,500, due mainly to evacuation and war service.

In spite of the ordeal caused by V.1 and V.2 and the continued strain of war, the general health of Londoners remained on the whole satisfactory. Tables analyzing civilian air-raid deaths in London show that 17,811 civilians were killed in the administrative county up to the end of 1944. There were 814,498 dwellings in London when the war started and of these 709,518 were affected by bombing, about 70,000 being completely destroyed, 56,000 rendered uninhabitable and 66,000 seriously damaged. 48,709 persons injured by bombing during the war were conveyed to hospitals or first-aid posts by the London Ambulance Service.

During the war years there were about 660 bombing incidents at the London County Council's hospitals, affecting all but 3 of the total number of 100 hospitals. At no time, however, had urgent cases to be refused admission. 17 of the hospitals had at various times to be evacuated and closed temporarily because of damage. 257 patients were killed in air raids (out of a total of 1,200,000 patients admitted during the period) and 62 hospitals staff were killed. 5,000 hospital beds were destroyed.

About 8,700 patients were evacuated from the Council's hospitals during 1944 to hospitals in the provinces and, as part of the scheme, the Council, on behalf of the Ministry of Health, administered 4 hospitals entirely new to the Council in North Wales, Yorkshire, Northumberland and Ayrshire.

The maternity death-rate in London is still decreasing, and in 1944 reached the record low level of 1.7 per 1,000 live births. The maternity death-rate has in fact fallen by more than half since 1934.

There were less births (44,554) in 1944 than in 1943 (45,030) and, mainly on account of air raids, more deaths (41,077) than in 1943 (39,322). The birth-rate steadily increased during the war years, although the marriage-rate has decreased since 1941.

The infant mortality rate, 51 per 1,000 live births, was the same as in 1943.

The report makes an interesting comparison between the vital statistics of London and New York, showing that the London birth-rate is at present increasing while the New York birth-rate has fallen since 1943; that the London death-rate is higher than the New York death-rate; that the infant mortality-rate for London is substantially higher than that for New York; that the maternal mortality rate is about the same for both cities; that the accident death-rate, including street accidents, is about the same in both cities; that mortality from pulmonary tuber-

culosis in London is about twice, while that from other forms of tuberculosis is between three and four times, that in New York; and that the death-rate from influenza is much higher in London than in New York.

The nutritional condition of the great majority of London school children still continues to be satisfactory and is, in fact, better than in 1938, a great tribute to the work of the Ministry of Food. Following the evacuation of children from London in 1944 there was no recurrence of the complaints about their condition which were received in 1939. On the contrary, many letters referred to the surprisingly good health and cleanliness of the children, especially in view of the state of London and the shelter life which then prevailed.

4,065 children were immunized against diphtheria during 1944 by the medical staff of the London County Council, making a total of 65,199 children immunized since 1940, in addition to those immunized by the medical staffs of the Metropolitan Borough Councils. By July 1944 about 68% of London elementary-school children had been immunized.

There was a decrease in the number of new notifications of tuberculosis (5,729 in 1944 compared with 5,848 in 1943) and also in the number of deaths (2,310, or 0.94 per 1,000 population, compared with 2,460). Miniature mass radiography examination of various sections of the public, for the early diagnosis of the disease, was continued during 1944. 46,671 miniature films were taken and 1,795 large films (about 3.85% of miniatures) were taken in those cases where the miniature film disclosed any significant abnormality. Particulars are given (page 26) of the classification of the large films. For every 10,000 persons who volunteer to have their chests *x*-rayed, 24 are found to be in need of sanatorium treatment. Over £120,000 was paid during 1944 in allowances to patients undergoing prescribed treatment.

There were 206 deaths from influenza in 1944 compared with 726 in 1943, when there was an epidemic in January of that year. Scarlet fever was appreciably less prevalent in 1944 than in 1943 and there were 7 deaths compared with 11 in the previous year. There were 2 notifications of smallpox in 1944.

There were 178,433 admissions during 1944 to the Council's public health hospitals. 13,050 births (12,612 live births) took place in the Council's general hospitals and, in addition, 5,924 confinements at home were attended by the Council's own midwives. (There were about 21,000 births a year in the Council's hospitals before the war.)

With regard to the Council's mental health services, there was a continued fall in the number of mental patients. During 1944 about 29,500 patients passed through the emergency (general) hospitals attached to the mental health services.

The report pays a tribute to the staff of the Council's health services who, despite continued, and in many respects more acute, war-time difficulties, kept the services running efficiently.

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A NEW UNIT FOR RESEARCH INTO THE COMMON COLD

It is announced that a "Common Cold Research Unit" has been established by the Medical Research Council and Ministry of Health, and that the work of the unit will have started by July, 1946. The Ministry of Health and the Medical Research Council point out that the problem of the common cold is a particularly complex one, made more difficult because, apart from chimpanzees, which are unsatisfactory for experimental purposes, it has not yet proved possible to study it in animals.

Progress towards the discovery of effective means of preventing a number of other diseases has not been made until some way of observing the disease in animals became available. For example, an effective vaccine against yellow fever became possible only when rhesus monkeys, and later mice, were found to be susceptible to the virus of the disease. Similarly, not until it was discovered that ferrets were susceptible to influenza virus was any progress made with the study of influenza. Therefore, the first objective of the present investigations into the common cold is to find a susceptible animal or, better still, some other laboratory technique which will permit a scientific approach to the problem.

As a check on their laboratory studies, workers at the National Institute of Medical Research will, at least for the time being, require to test on human volunteers the cold-producing activities of materials they are studying. Volunteers will first be isolated until it is certain that they are free from infection. Then, after a few days' quarantine, their noses will be sprayed with material to see whether or not it contains a virus. While these observations are being made—for a period of 10-14 days in all—the volunteers will be out of contact with the outside world and each other except that, to obviate the boredom of solitary confinement, they will normally live together in pairs. Isolation will not involve complete loss of freedom, for the volunteers will be allowed to move about the countryside around the hospital, provided they avoid all human contacts, and will live in restful and comfortable holiday conditions. Volunteers are already being recruited from among university students. If more are needed later, an appeal will be made through suitable organizations. Volunteers must be carefully selected, because special qualities are needed and an exact discipline must be maintained. For this reason the Medical Research Council is selecting its own recruits, and applications from the general public cannot be entertained.

Progress towards the solution of the many problems which face the medical scientists undertaking this research work is likely to be slow, and it would be unwise to expect any spectacular advance, at any rate in the near future.

* * *

More about early Ether Inhalers

Since we published, in our last number, a considerable amount of material on the history of anaesthesia, including the development of inhalers[1], we have received an interesting paper on "Ether inhalers in early use", by Dr. William W. Ford[2], of Baltimore.

Dr. Ford reproduces figures of the following inhalers: Morton (USA, 1846); Morton & Gould (USA, 1847); Squire (England, 1847); Gilbertson (England, 1847); Tracy (England, 1847); Smee's Portable[3] (England, 1847); Salt (England, 1847); Gallard (country of origin not stated, 1847); Snow[4] (England, 1847); Lüer (France, no date); and Charrière (France, 1847). Several other inhalers are referred to in the text. An interesting point made by Dr. Ford is that trials of ether in France preceded those in England by a few days. On 15 December 1846, an unsuccessful demonstration of ether anaesthesia took place at the Hôpital Saint-Louis, Paris.

[1] See especially *BMB* **827, 829, 830**

[2] *New England Journal of Medicine*, 1946, **234**, 713-726

[3] This is a different model to that figured in *BMB* **830**

[4] A different apparatus to that figured in *BMB* **827, 829**

The Library

Publications discussed or listed in this section may be borrowed by inquirers resident in the United Kingdom on application to the Editor.

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A FRENCH WORK ON VIRUS DISEASE

Professor C. Levaditi's latest book (*Précis de virologie médicale*, 250 pages, 142 illustrations, Paris, Masson, 1945) is designed to give the physician and student some insight into current work on the virus diseases of man. It is well printed and very freely illustrated, though, as is still the way with the French, the histological aspects are portrayed in drawings rather than in photographs. The reader will obtain a useful survey, especially of the work of Levaditi's own school; the allotting of pages to the various viruses is rather closely related to the attention they have received in the author's own laboratory. There is a freely-illustrated chapter on virus techniques.

At this time many Continental workers are visiting Britain and the United States to acquaint themselves with recent developments in research from which they have been cut off since 1940; 1945 seems accordingly a singularly unfortunate moment for a Continental worker to have attempted to produce a review of such a rapidly-moving subject as virology. One sees, for instance, no mention of Hirst's haemagglutinin test in influenza, described in 1941 and now the most generally useful laboratory method for workers on that disease. Of references to authors there are many, but these are all, whether by design or oversight, left "in the air." We read "Levaditi (1925)" or "Blanc (1921)," but look in vain for a bibliography in which to discover where to pursue our studies of these authors' writings.

897

RADIOBIOLOGY IN FRANCE

In a contribution[1] to the "Collection des Actualités Radiobiologiques" published under the general direction of MM. Dognon and Biancani, Dr. J. Lavedan has given a brief summary of the action of penetrating radiations on the cells of normal tissues. The book is in two parts. In the first (48 pages) the author discusses the relative importance of the effect on nucleus and cytoplasm (chapter 1); the changes in radiosensitivity associated with various biological functions of the cell such as mitosis, segmentation, metabolism and so on (chapter 2); and then "inverting the problem" he describes the action of radiation on particular activities of the cell, e.g. mobility, reproduction, respiration, permeability, etc. (chapter 3). Here he quotes Lacassagne's description of the dissociation of cell functions produced by radiation as a "physiological microdissection" peculiar to this agent.

The second part of the book (57 pages) deals with the physical factors of radiation and includes some consideration of the mechanism of the action of radiation (chapters 1 and 4); the significance of wavelength and the time-factor (chapter 2); radiation-induced mutations (chapter 3); and a summary of conclusions (chapter 5). This is followed by a short addendum of six pages on recent ideas about the mechanism of the action of radiation which might more conveniently, for the reader at least, have been included in earlier sections of the book.

The bibliography is disappointing. Nearly 300 names are mentioned in the text, but only 96 references, comprising 65 names, are quoted in full. Instead, the reader is referred to Lamarque's recent book[2] where, he is told, he will find a very complete literature. *F. G. S.*

[1] *L'action des radiations sur la cellule normale.* Paris, 1945. 128 pages.

[2] Lamarque, P. *Les bases physiques et biologiques de la roentgenthérapie.* Paris, 1942.

898

YELLOW FEVER

In 1932 members of the Rockefeller Foundation working on yellow fever in Brazil introduced the viscerotome to obtain specimens of liver for diagnosis of fatal illnesses. This method has proved to be of inestimable value in studying the epidemiology of yellow fever, especially the jungle type.

In 1935 the French Government commenced similar studies in French West and Equatorial Africa in order to define the endemic areas and detect any spread of the disease in an unrecognized form. J. Bablet has examined several hundred specimens of liver from suspected cases collected in these regions from 1935-43. As a result of these studies, and in order to aid the physicians and pathologists encountering cases suspected to be yellow fever, he has (*La fièvre jaune*, Paris, 1945, 69 pages) summarized briefly the clinical picture and differential diagnosis; the laboratory tests used in diagnosis; the best methods of preparing tissues for histological examination and the specific pathological lesions and differential diagnosis of them.

Bablet advocates the use of the viscerotome in all patients, febrile or non-febrile, jaundiced or not, who die in less than 11 days from the onset of their illness. Pieces of liver and kidney where possible are fixed in 10% formalin and sent to the nearest pathological laboratory. The advantage of the viscerotomy service is that personnel with no knowledge of medicine can collect the desired specimens.

As a result of the examination of his own material and the large collection of specimens in Rio de Janeiro, Bablet considers that there is a histological picture which is specific for yellow fever. The lesions, which are the same as those previously described from West Africa and South America, consist of generalized fatty degeneration and a coagulation hyaline necrosis (Councilman lesion) and chromatolysis of the nuclei of the parenchymal cells chiefly in the mid-zone of the lobule. Once more attention is drawn to the frequent occurrence of chronic hepatitis among the African natives and Syrian traders who have lived in the country many years. This lesion frequently influences the usual clinical picture of yellow fever, resulting in death in 3 to 4 days with little or no fever. The previous histological changes mask those of yellow fever. Councilman lesions are rare and there are extensive recent haemorrhages.

The author stresses the usefulness of the viscerotome in providing information of the incidence of other lesions of the liver in the courses of the yellow fever studies and also as a routine method for studying hepatic lesions in disease of other tropical countries. *F. O. MacCallum*

899

FRENCH VIEWS ON THE PROLAPSED INTERVERTEBRAL DISC

In *Sciatiques et lombalgies par hernie postérieure des disques intervertébraux* Prof. D. Petit-Dutaillis and Dr. S. De Sèze present the first French monograph on the surgical aspect of sciatica. It is based on 50 of their own cases, and will certainly be of great value to the French-speaking medical world.

From the clinical point of view they are in almost complete agreement with the Anglo-American authors as regards history, symptoms and signs. Myelography is employed in every case, but in recalcitrant and chronically incapacitating cases of sciatica the operation is indicated anyway, as the root compression may be due to "funiculitis with root oedema, isolated hypertrophy of the ligamentum flavum, arachnoiditis or even gross spondylarthritis." Fully aware of the risks of lipiodol, the authors advocate its removal by making a small incision into the theca at the end of the operation, in order to prevent what they call "huilomes" ("oleomata").

The operation is done under local and intra-arachnoid anaesthesia, occasionally supplemented by pentothal. They favour a large exposure, including bilateral ablation of two laminae, and of the articular processes. Only large protruding fragments are removed. In recent cases they have practised posterior rhizotomy. This is advocated in spite of the claim that no true relapses were observed among 50 cases of which nearly all returned to their work. Minor complaints, such as

backache, are admitted to occur, but only for short periods. The indications for osseous grafts are considered to be practically non-existent.

Conservative treatment should always be tried first, except in cases of paralysis and cauda equina lesions. If after adequate bed-rest and the other usual measures, there is no improvement, a surgical belt is often employed; in cases of marked spinal deformity this is preceded by the application of a plaster jacket to be worn for one or two weeks.

A well documented and illustrated discussion of the possible aetiology, anatomy and pathology of the lesion is a great asset to the book, as are the numerous radiograms and operative sketches. The lucid presentation should acquaint many with a sound way of dealing with an incapacitating malady, for the understanding and treatment of which these two authors have done outstanding pioneer work in France.

F. Schiller

900

BIOENERGETICS

Samuel Brody's *Bioenergetics and growth*[1] is a monumental work and will become a classic. In just over a thousand pages the author presents succinctly and yet comprehensively an integration of the results of the researches of the Agricultural Chemistry Division of Missouri Agricultural Experiment Station concerning the quantitative energetic efficiencies of agricultural processes such as those concerned in the maintenance and in the production of meat, milk, eggs and muscular work, along with the principle of diminishing returns and its relation to planes of nutrition. In addition, consideration is given to the relation of the speed with which these transformations occur to the efficiency of the process, and to the influence of the size of the producing animal on the efficiency and profit of the productive enterprise. The book is also concerned with nitrogen metabolism, with growth, development and aging, and with the catalysis of these processes.

The one hundred and fifty-fold increase of the human population in the past 100 years in the USA is held to be a direct consequence of the progress in agricultural production.

Here we have both scientist and philosopher, for the author has felt the need for a unifying principle when writing this immense work which would interrelate all the various components. The concept of physiological regulation as enunciated by Sherrington when he stated that "the organism acts as though it desired to maintain itself", or, more recently, by Cannon when he coined the term "homeostasis", comes nearest to meeting the need for such a generalizing principle. The philosophic note in which this remarkable book ends is that the future trends of human behaviour and social phenomena, although unpredictable and the despair of the social scientist, are at the same time the hope of humanity; for man is given an opportunity to mould his destiny that is not permitted to other species that are subject to more determinate, orderly laws.

D. P. Cuthbertson

901

TRYPANOSOMIASIS: A NEW MONOGRAPH

In the abstracts which appear month by month in the *Tropical Diseases Bulletin* and the *Bulletin of Hygiene*, and in the *Bulletin of War Medicine* during the war, the Bureau of Hygiene and Tropical Diseases records the current literature on subjects coming within its fields of interest. From time to time the Bureau has been asked for information on some particular branch of medical work to be collected together in the form of a monograph for the greater convenience of persons concerned with a special problem. This is a service, which, because of its day-to-day abstracting organization, the Bureau is favourably placed to perform. Such a monograph has recently been compiled for the Tsetse Fly and Trypanosomiasis Committee appointed by the Secretary of State for the Colonies, and though designed to meet a particular need it is thought that its publication may prove useful to a wider public. "A survey of recent work on trypanosomiasis and tsetse flies" is therefore now published as *Bureau of Hygiene and Tropical Diseases: Review Monograph No.* 1, and provides a brief statement of the work done, and some of the opinions expressed, by those who have worked at the different problems concerned with trypanosomiasis since 1931. The monograph is obtainable from the Bureau, Keppel Street, London, W.C.1, price 7s. 6d. [£0.375]. 81 pages, 1946.

[1] *Bioenergetics and growth, with special reference to the efficiency complex in domestic animals*, by Samuel Brody. New York, Reinhold Publishing Company 1945. 1023 pages. $8.50.

902

A RUSSIAN SURGICAL CLASSIC

N. Pirogov: *The foundations of general war surgery.* 2 vols. Moscow, 1941. [In Russian.]

Seventy-five years ago, Pirogov published his classic work on "The foundations of general war surgery", basing his studies on his experiences in the Crimean War and the Caucasian Expedition. In 1941 these two historic volumes were republished in a new edition by Prof. N. Burdenko. Burdenko states in his foreword that this work is a most valuable contribution to war surgery, although it was written so many years ago, and that it is still a fundamental guide to surgeons all over the world. Pirogov's voluminous treatise deals with the study of traumata and of the general reaction of the body to trauma, with the local reactions to trauma, with the study of wounds, their course and complications; further, with the study of gun-shot wounds, complicated and uncomplicated, with the treatment of wounds of soft tissues, infected and not infected, with the study of plaster bandages and, finally, with wounds of cavities. If one remembers that 75 years ago all these subjects were hardly investigated and described and also remembers the primitive conditions available in those days, one can judge what a tremendous task Pirogov undertook and how magnificently he achieved his object.

H. W. Swann

903

SOME RUSSIAN SURGICAL WORKS PUBLISHED DURING THE WAR

C. L. Schneider: *Transplantation of skin by the sieve method.* Novosibirsk, 1944. [In Russian.]

The author strongly advocates the method of skin transplantation described by the American surgeons Dragstedt and Wilson in 1937. The method consists of a transplantation of the whole thickness of the skin (without the fatty layer), which is perforated in many places to resemble a sieve. The author recommends this method even in emergency operations and also describes many other operations, where this method has been most successful. The author also devotes a special study of the way the defect should be prepared for the transplantation. The book is based on personal experience during a period of 6 years and describes not only the successful cases, but also the failures.

V. A. Negovsky: *An experiment in treating conditions of agony and clinical death at the front line.* Moscow, 1943. [In Russian.]

This book is a sequel to the author's previous study of the restoration of life functions of the body which is in a state of agony or clinical death. The experiment was carried out at the front line during a period of four months. In all 51 cases of agony and clinical death were treated and in 12 cases there was a complete cure. In 37 cases there was only a transient effect and the patients died later on account of the severity of their wounds. Only 2 cases did not respond to any measures of resuscitation. The author gives a detailed account of every case. He emphasizes that the first three minutes, in which a resuscitation can be attempted, are the most vital. The thoroughness and efficiency of the preliminary preparation is most essential.

V. A. Negovsky: *The restoration of life functions of the body which is in a state of agony or clinical death.* Moscow, 1943. [In Russian.]

Biological or irreversible death is usually preceded by a period of clinical death, which is diagnosed from the moment of

cessation of the heart action and respiration. The aim of this book is a study of certain aspects of the pathology and physiology of the dying process and the subsequent restoration of the life functions of the body. There is a detailed study of the functions of respiration and circulation of the blood, of the metabolism and the resistance of the central nervous system to anaemia. The experiments were made on animals, which were subjected to complete loss of blood. There are also some experiments on the resuscitation of asphyxiated new-born babies.

I. A. Kopylov : *Amputations and the amputated.* Leningrad, 1943. [In Russian.]

This is a short, but rather detailed, account on amputations. The author first gives a historical survey and describes what the imperfections of amputations were in the past and then proceeds to outline how the optimum results can be obtained, and how amputations should be done at the front so as to facilitate the work of the surgeons in the rear. One chapter deals with the transplantation of the skin to cover up defects and another with the problem of how to shorten the period of hospitalization of the amputated.

F. Salkindson : *Physiotherapy in war injuries.* Leningrad, 1943. [In Russian.]

In the general part of the book the author deals with the physiotherapy which can be provided near the front line and at the different stages of evacuation of wounded and also with the equipment which is necessary for that purpose. The special part of the book gives a review of a large number of injuries where physiotherapy is essential. It deals particularly with the use of physiotherapy in gunshot wounds of all kinds, gas gangrene, injuries to bones and joints, congelations and burns, and finally to injuries of the nervous system. The book also gives a complete list of all necessary forms for statistical purposes.

H. W. Swann

BOOKS FROM FRANCE

904

B. Fey & P. Truchot : *L'Urographie Intra-Veineuse.* Masson et Cie, Paris, 1944. 209 pages.

This is a valuable treatise on the subject of excretion urography. The greater part of it consists of reproductions of *x* rays illustrating normal and diseased conditions of the urinary tract, each with an adjoining note which explains the points to which attention is directed. In the text a full account is given of the origin of this method of investigation, the technique to be adopted, possible accidents which may follow imperfections of technique and a discussion upon what may be expected to be derived from intravenous urography. There are chapters on each of the important renal diseases, and in these the special uses of the method are discussed. It is rightly pointed out that of all methods of urological investigation this is the least harmful, the least unpleasant, and the most illuminating. Professor Fey in a foreword remarks that the precise interpretation of the radiographs requires an expert with specialized knowledge ; urologists everywhere will agree with him, for they know full well that first-class *x* rays are essential and that in many instances a diagnosis can only be established by consultation between the urologist and the radiologist concerned. The authors have employed as an injection 50 cm.³ of tenebryl of 30% strength; a table is given of suitable doses for children. A chapter is devoted to the method as a test of renal function and its great value in this respect is emphasized. Attention is frequently drawn to the values of the test of von Lichtenberg, which is a comparison of the relative shadow densities of the two sides, and the test of Ravasin which studies specially the time of appearance of the drug in each kidney, the earlier shadow indicating the better kidney. These two tests are usually but not always found to be in agreement and judgment upon the results of them must be nicely balanced. Little space is given to the bladder-shadows produced in excretion-urography and whilst it is certain that cystoscopy is a more accurate method, something further might have been said as to the value of this, for it not infrequently shows the need of further investigations which might otherwise be regarded as superfluous. English readers will find the *table de matières* inadequate, it is what they will call merely a list of " contents ". A true index of subjects, methods, diseases and names would add to the value of the book.

It is notable that this volume was produced in Paris in 1944. The type is excellent, the paper of good, though not the finest, quality, and suitable for the reproduction of radiographs. English writers who have experienced great difficulties in getting their books published during the war will be amazed that this was possible during the German occupation. Fortunately it has been done and a valuable book for study and reference has resulted.

Edwin Sidi : *Les accidents cutanés des teintures capillaires : La sensibilité à la paraphénylènediamine.* Flammarion, Paris, (?) 1945. 152 pages, 21 figures. 195 francs.

The author has had the opportunity of examining nearly 300 cases of skin affections which could be proved to be due to hair dyes ; in almost every instance the dye used had paraphenylendiamine as its base. The book is divided into five parts : I. General—Chemical and biological properties of dyes derived from aniline ; II. Clinical and therapeutical study ; III. The problem of pathogenesis and the tests ; IV. Prophylaxis ; V. Medico-legal aspects. The author lays particular emphasis on the importance of methods of protection and the advice to be given to hairdressers and others whose livelihoods are affected by their sensitivity to such dyes. There is a bibliography of some 50 references and the book is well illustrated.

Pierre Mollaret & Ivan Bertrand : *L'Hypertonie de décérébration chez l'homme.* Masson, Paris, 1945.

This monograph by two members of the staff of the Salpêtrière was inspired by the case of a man with so-called decerebrate hypertonia following encephalitis, and lasting 17 years. A detailed study of the case forms the central part of the book, the other two sections comprising an exhaustive examination of previous work on this subject by physiologists and clinicians. A comprehensive bibliography is appended.

Rémy Adrien Delauney : *La pénicilline.* Presses Documentaires, Paris, 1945. Second edition.

The author sets out to collect, and present in a small volume accessible to any educated reader, the essential facts in our present knowledge of penicillin. After a brief historical note, he describes the culture of penicillium, the extraction, constitution and experimental and therapeutic action of penicillin in some detail, concluding with a chapter on " Other bactericidal substances of fungoid or bacterial origin." There is a bibliography of 115 references.

L. Tavernier & Ch. Godinot : *Traitement chirurgical de l'arthrite sèche de la hanche suivi de travaux de la Clinique Orthopédique de la Faculté de Lyon.* Masson, Paris, 1945.

This work, by the professor of paediatric and orthopaedic surgery at Lyons and his co-workers, is based on the authors' long clinical experience. The first and main part deals with the surgical treatment of rheumatoid arthritis of the hip. After describing the condition in detail, the authors consider the various types of operation they have used in the course of 25 years, ending with a chapter on the indications for the different operations. This part is completed by a list of 108 case histories. The second part deals more briefly with the surgical treatment of rheumatoid arthritis of other joints, while the third part s a collection of articles describing the authors' work on orthopaedic surgery during the last few years. Some of these have not been published before, though most of them have already appeared in journals. The book is well illustrated, but has no index, and the only bibliography is a short one attached to one of the articles in the third part.

Hémoptysies non tuberculeuses et hémoptysies sans causes. (G. Doin & Cie. Paris, 1945), by Jacques Lecœur.

The author has made a systematic study of 65 cases of non-tuberculous haemoptysis and here presents the results of diagnosis by means of bronchoscopy and lipiodol bronchography. The first two chapters comprise preliminary discussions of the diagnostic problems of haemoptysis, and the relative value of these two methods of diagnosis ; the subsequent chapters (IV-IX) are devoted to a detailed and classified study of results in

the author's own cases. The causes of 55 of these were revealed by bronchoscopy; of the remaining 10, 5 were identified by means of lipiodol bronchography, 5 alone being still unidentifiable after both methods had been used.

905

BOOKS IN SPANISH

Oxigenoterapia (Manuel Marín, Barcelona, 1945), by J. Chabas, editor of the *Revista de Higiene y de Tuberculosis*, will, writes Dr. Marañon in his foreword, do much to increase the prestige of this valuable therapeutic auxiliary, which has not hitherto received all the recognition it deserves. Dr. Chabas devotes 30 pages of his book (Parts 1 and 2) to a discussion of the theory of oxygen therapy, covering such problems as anoxia in respiratory and circulatory pathology, basal metabolism and the pathogenesis and diagnosis of endocrine disorders, acid-base equilibrium and blood *p*H, and many others. The third part gives a preliminary description of the various types of apparatus, the technique of treatment, the possible accidents and risks which have to be considered and the effects of hyper- and hypoxygenation. The fourth and main part deals with oxygen therapy in diseases of the respiratory system, the circulatory and digestive apparatus, and the nervous system, in gynaecology and obstetrics, in infectious diseases, and in surgery, and a final chapter considers its possibilities in a miscellaneous selection of diseases from cancer to sprue. Brief sections on ozone and carbon dioxide therapy are appended.

Plantas medicinales aromáticas o venenosas de Cuba (Habana, 1945), by Dr. Juan Tomas Roig y Mesa, chief of the chemistry department of the Agricultural Experiment Station at Santiago de las Vegas, is one of a series of technical publications of the Cuban Ministry of Agriculture. As stated in the foreword, this 2-volume monograph seeks to give as complete and exact an account as possible of the medicinal and poisonous plants of Cuba, to provide students of botany, pharmacy, medicine, agriculture and veterinary science with a work of reference, to stimulate Cuban scientists to further study of the local medical and toxicological flora, and finally to encourage the cultivation and development of indigenous and acclimatized medicinal plants. A preliminary grouping of plants, according to their uses, precedes the main body of the work, which gives details regarding synonyms, habitat and distribution, botanical descriptions, therapeutic properties and references for further reading, for over 1,500 plants. Three separate indexes (*a*) of common Cuban names, (*b*) of scientific names and (*c*) of names in common use in other American countries, complete this comprehensive study.

La penicilina y sus aplicaciones en oftalmología (Mexico, 1945), by Antonio Ros, represents the content of a lecture delivered by the author at a meeting of the Sociedad de Médicos of the Hospital Español, Mexico, and "sent to the printers without further corrections or additions". Brief introductory sections on the clinical importance of penicillin and the history of its discovery are followed by a review of its properties, clinical value, effects, toxicity and dosage, and finally by a discussion of its applications in ophthalmology—particularly as a prophylactic medium in the surgery of the eye—in relation to the author's own practical experience. Illustrative case-histories and a bibliography complete this concise account of the new drug.

906

PUBLICATIONS FROM BARCELONA ON THE PROBLEM OF THE ABANDONED AND DELINQUENT CHILD

The following have been received from Barcelona:

Manich, F. & Córdoba, J.: *Higiene social de la infancia*, Barcelona, 1943.

Albó Martí, R.: *Cuatro colonias agrícolas para menores moralmente abandonados*, Barcelona, 1942.

Albó Martí, R.: *El tribunal tutelar de menores de Barcelona en el año* 1943, Barcelona, 1944.

Albó Martí, R.: *El tribunal tutelar de menores de Barcelona en los años* 1939 *y* 1940, Barcelona.

Albó Martí, R.: *Estadística de los factores influyentes en el extravío de los menores ingresadas en* 1944, Barcelona, 1945.

Boletín de Actividades de la Junta Provincial de Protección de Menores, Barcelona, 1945.

907

JOURNALS RECEIVED

Vol. 1, No. 1 of the *Journal of the Palestine Arab Medical Association*, "the first Arab medical periodical to be published in Palestine," appeared in November 1945. In addition to the Arabic section it contains five original articles, a "General Medical News" section and two brief reports: "Comparison of various types of local treatment in a controlled series of experimental burns in human volunteers" and "Intradermal use of convalescent serum" in the English language. As stated in the foreword, this Journal is designed to meet "a long-felt need among Arab medical men for a local periodical in which can be recorded for study and reference the results of their research and experience, especially in endemic and other diseases peculiar to the country and to the Mediterranean basin".

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Clínica Tisiológica (Rio de Janeiro). Vol. 1 (1944), which has just reached us, reports (in nine signed articles) the scientific activities of the clinical staff of the Hospital Miguel Pereira, which has recently developed from a hospital for the surgery of chest disease into a centre for the diagnosis and active treatment of pulmonary tuberculosis.

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Ciencia e Investigación (Buenos Aires): The twelve numbers comprising vol. 1 (1945) of this monthly journal, published under the auspices of the Asociación Argentina para el Progreso de las Ciencias, have recently been received. The journal is intended to give a general account of present-day developments in the exact sciences, not to publish highly specialized articles in any particular field. Each number contains three or four signed articles, a book review section, a number of brief notes on recent researches in various parts of the world, and information on the activities of the Asociación. This is a most stimulating and attractively produced scientific monthly, which should be of interest to workers in all branches of science.

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Cirugía del Aparato Locomotor (Madrid). The first number of Vol. II (January 1945), which has just reached us, contains 6 signed articles and short sections devoted to reviews of Spanish medical books and to abstracts of articles from foreign journals respectively. The journal is published quarterly.

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Archivos de la Sociedad Oftalmológica Hispano-Americana (Madrid). Vol. 5, No. 10 (October 1945) of this monthly journal published under the auspices of the Consejo Superior de Investigaciones Científicas, has recently been received. In addition to 8 original papers, 2 clinical notes and summaries of a series of 5 lectures on the vascular pathology of the retina, abstracts of papers read at the various sessions of the Society's twenty-third congress are given. A final section comprises abstracts from foreign literature.

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Anales Españoles de Odontoestomatología (Madrid): This monthly journal is now in its fifth year of publication. The December 1945 number which has just been received contains 3 original and 2 review articles and brief bibliographical and abstracting sections.

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Prótesis (Buenos Aires). This quarterly journal published by the Sociedad Odontológica Argentina de Prótesis is now in its ninth year of publication and is excellently produced and illustrated. No. 28 (March, 1945), which has just been received, contains 7 original articles and short abstracting and bibliographical sections.

Publicaciones del Instituto Antituberculoso "Francisco Moragas" (Barcelona). Volume VI (1945) comprises two sections: the first reproduces the text of a course of 6 lectures, given in April 1944, under the heading "Physiology of the Neuromuscular System of the Lung"; the introductory lecture, by C. Zalabarder, bears the title of the heading, while the fifth and sixth lectures by the same author deal with "Atelectasis" and "The Lessons of Thoracoscopy and Monaldi's Method" respectively. The remaining lectures of the course are "Respiratory Physiomechanics and its Value in the Pathology and Therapeutics of Pulmonary Tuberculosis", by J. Argemí Lloveras, "Clinical Disagreement with Mechanical Ideas", by E. Alegret, and "Anatomy and Physiopathology of the Pulmonary Regions," by I. Blajot Pena. In the second section H. Sanjuán Nadal gives an account of his researches on the biology of Koch's bacillus under the title of "Some Problems in the Bacteriology of Tuberculosis", illustrated by a number of photomicrographs, and accompanied by a bibliography.

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Revista Ibérica de Parasitología (Granada): This quarterly publication from the Instituto Nacional de Parasitología of the University of Granada is sponsored by the Consejo Superior de Investigaciones Científicas. The January-April 1945 issue (Vol. V, Nos. 1 and 2), which has recently been received, contains a lengthy thesis on bowel obstructions caused by *Ascaris*, an article on the susceptibility of domestic and wild animals to *Spirochaeta hispanica*, and Part II, Chapter III of a compendium of Iberian helminthology, the heading of which is "Familia *Taeniidae Ludwig* 1886".

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908

OTHER BOOKS RECEIVED

Bariéty, M. & Brocard, H.: *Les septicémies à staphylocoques*. 252 pages. Paris, J.-B. Baillière, 1945

Cambessédès, H. & Boyer, J.: *Hygiène des institutions de plein air*. 172 pages. Paris, J.-B. Baillière, 1946

Chauchard, P.: *Le système nerveux et ses inconnues*. 126 pages. Paris, Presses Universitaires de France, 1944

Courrier, R.: *Endocrinologie de la gestation*. 399 pages. Paris, Masson, 1945

Duhamel, G.: *Régimes alimentaires usuels de l'adulte*. 169 pages. Paris, J.-B. Ballière, Paris, 1946

Gouin, J.: *La leucocyto-réaction. Elément de diagnostic et de thérapeutique. Applications en syphiligraphie, dermatologie et médecine générale*. 252 pages. Paris, Masson, 1945

Guillain, G., Bertrand, I. & Gruner, J.: *Les gliomes infiltrés du tronc cérébral*. 286 pages. Paris, Masson, 1945

Huriez, C., Dumont, R., Patoir, G. & Leborgne, J.: *Les gonococcies sulfamido-résistantes*. 61 pages. Paris, Masson, 1945

Kolff, W. J.: *De kunstmatige nier*. 200 pages. Leiden, Kok, 1946

Mallet-Guy, P. & Maillet, P.: *Hypoglycémies spontanées. Le traitement chirurgical de l'hyperinsulinisme*. 102 pages. Paris, Masson, 1944

May, R. M.: *La formation du système nerveux*. 300 pages. Paris, Gallimard, 1945

Milian, G.: *La syphilis occulte*. 181 pages. Paris, J.-B. Baillière, 1946

Monnier, J.: *La pénicilline à la portée du praticien et son emploi dans le traitement des maladies vénériennes. Pénicilline et syphilis. Pénicilline et gonococcie*. 148 pages. Paris, J.-B. Baillière, Paris, 1946

Peña, A. y E.: *La resección transuretral de la próstata*. 150 pages. Madrid, Ediciones Morata, 1944

Policard, A. & Galy, P.: *Les bronches. Structures et mécanismes à l'état normal et pathologique*. 191 pages. Paris, Masson, 1945

Sanz Ibáñez, J.: *Poliomielitis experimental*. 127 pages. Madrid, Consejo Superior de Investigaciones Científicas, 1944

Sidi, E.: *Les accidents cutanés des teintures capillaires. La sensibilité à la paraphénylènediamine*. 151 pages. Paris, Editions Médicales Flammarion, 1945

Suarez, F. G.: *La carditis reumatica (carditis nodular estreptofocal recidivante). Errores de la doctrina clasica. Tratamiento profilactico de las recidivas*. 235 pages. Madrid, Ediciones de los Estudiantes Espanoles, 1945

Uriburu, J. V.: *Oclusión intestinal. Tratamiento medico mediante el sondeo aspirador y medidas asociadas. Con un apéndice sobre la aspiración en cirugia gástrica*. 377 pages. Buenos Aires, El Ateneo, 1945

Varela Fuentes, B., Recarte, P. P. & Graña, A.: *Alergia en la practica clinica*. 974 pages. Buenos Aires, Espasa-Calpe Argentina-S.A., 1946

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Films

909

Personnel Selection in the British Army in 1944: Recruits

made by Shell Film Unit, 1945, in co-operation with the Directorate of Selection of Personnel, War Office; owned by Central Office of Information; 16 mm. sound, 2185 ft. [660 m.]; 35 mm. sound, 5446 ft. [1630 m.]; black and white; 56 minutes.

910

Personnel Selection in the British Army in 1944: Officers

made by Shell Film Unit, 1946, in co-operation with the Directorate of Selection of Personnel, War Office; owned by Central Office of Information; 16 mm. sound, 3591 ft. [1080 m.]; 35 mm. sound, 8898 ft. [2670 m.]; black and white; 90 minutes.

These two important films are the second and third of the "Report from Britain" series—the first was Neuropsychiatry.[1] They are made for audiences with psychological training but, though their appeal is greatest for psychiatrists, they would be understood and enjoyed by anyone interested in the problems of selecting candidates for jobs, or in vocational guidance.

Personnel Selection: Recruits shows how recruits are assessed during their first two weeks in the British Army so that they may be posted to the type of job for which they are best fitted and in which they will be most useful and happy. The scheme is explained to the recruits by a PSO (personnel selection officer). Then in classes, supervised and guided by sergeant instructors, they do a series of six tests. For one of these, the progressive matrices test, the amount of earlier formal education is unimportant; others, for example an arithmetic test, reflect previous education as well as innate ability, and a test of physical agility is included. A test originally designed for clerks only, but found to be more widely revealing and useful, is checking a series of items in two differently arranged lists.

[1] [For review, see *BMB* 774/9.—Ed.]

The performances of large numbers of recruits in these tests are referred to and illustrated by a distribution curve. They have been classified into 5 groups; group 1 includes the top 10%, group 2 the next 20%, and so on.

According to the group into which his marks in each of the six tests comes, the recruit completes the battery of tests with six selection group (S.G.) marks. Each job in the Army has been studied by a "job analysis" to discover the qualities necessary in a man to carry it out. All jobs are grouped into 7 categories, motor-driving, signalling, clerical, general duties, etc., and each of these has minimum SG marks. But these tests do not give enough information for satisfactory posting to the specialized units, and the recruits go on to a further series of tests. In one they have to assemble simple tools such as a bicycle pump; another, which sifts out those suited to be signallers, involves noting similarities in morse sounds.

With their SG marks and special-test results before him, the PSO interviews all the recruits individually, and reviews and corrects the details they have earlier recorded about their education, work records and hobbies. Some recruits are referred to the psychiatrist (two psychiatric interviews are shown in this film). Everyone in the bottom grade of marks sees the psychiatrist; some have given an unfair impression of their qualities, some are mentally quite unsuited for Army life, some will go to make up smart and useful units in the Pioneer Corps, where they are among their peers and not given jobs beyond their powers. The psychiatrist also sees some of the outstandingly good recruits, for the PSO is always on the outlook for men likely to make good officers.

When the recruit has completed his tests and interviews, the PSO considers the results and sums up his qualities and aptitudes and makes first, second and third choice or recommendation of suitable postings for the man. In making these recommendations the PSO is guided by the needs of the Army at the moment, of which he is kept fully informed.

The report sheet on each man with his marks and the PSO's summary and recommendations goes to the War Office and here the data are transferred to a Hollerith punched card. Thousands of these cards are dealt with daily by a sorting machine which at any moment will give the number of men available with various combinations of abilities needed to fill the many units the Army has to keep up to strength.

Personnel Selection: *Officers* shows a group of eight candidates throughout their three-day stay at a WOSB (War Office Selection Board Unit). They have the scheme explained to them and make written answers to question papers ranging over many topics. From these answers a provisional estimate can be made of their capabilities. During the daytime they undergo field tests under military testing officers. Judgment as well as agility is needed for these, some of which are tackled in pairs and some in groups. Sometimes a group is left without a leader to see who provides the initiative; sometimes one of the group is put in charge to see how he can bring out the best of his team. In the evening, discussion-groups are unobtrusively watched by members of the selection Board. Three of the eight candidates are followed more closely and we understand why the preliminary meeting of the board asks that they should see the psychiatrist. Two unrehearsed psychiatric interviews are shown. These sequences are of great interest and they reflect great credit on the director and psychiatrist, for they convey the easy and unhurried way the psychiatrist feels his way from the candidate's remarks to further questions. The relation of the contributions of military testing officers, psychologist and psychiatrist to the work of assessment is conveyed by recurrent animated diagrams throughout the film. The president of the selection board interviews all the candidates himself and when all the interviews and tests are completed the board meets. The shots of this meeting show that while, as in older methods of selection, it is still the president of the board who makes the decision of accepting or rejecting a candidate, he now has not only the opinions of the military testing officers and the impressions gained at his own interviews with the candidates, but also the reports of psychologist and psychiatrist on the intellectual capacity and personality of each candidate. At the end of the course the group are asked for suggestions for improving the methods, and the unsuccessful candidates are told that they may try again at a later date.

These films show a social use of applied psychology which has obvious large implications in civilian fields, and though they deal with a complex subject, by first-class direction and the wise use of diagrams, they remain (especially the officer film) personal and vivid. *R. MacKeith*

911

Education of the Deaf

made by Data Film Unit, 1946; owned by British Council; 16 mm. sound, 1520 ft. [460 m.]; 35 mm. sound, 4680 ft. [1400 m.]; black and white; 52 minutes.

The film starts with a demonstration of the tragedy of the young otosclerotic shut off from her family, and then shows the greater tragedy of the child deaf at birth or rendered deaf in infancy. Without special care, the child would be doomed to be dumb and, therefore, virtually an idiot also. The adult can be helped by suitable deaf-aids selected for her by careful audiometer- and speech-tests, but the child is a more difficult problem. She is sent to a special school when 3 years old; here she learns first of all to copy her teacher's lip-movements, and then to make noises. As time goes on she learns to make speech-like noises, and by the time she is six can speak recognizably a large vocabulary, and understand much simple conversation by lip-reading. At seven years of age the class is divided into two halves, those with residual hearing who can appreciate the noise from amplifying earphones, and the totally deaf. Amplifier classes are shown, and then the advanced lip-reading classes, but even here lessons are taken entirely by speech. By 16 years the children have practically the attainments of their normal colleagues. They are taught trades (the school is partially self-supporting from the activities of its trade trainees) and a job is found for them. Many, in spite of complete deafness, have fine singing voices, and dance with a keen sense of rhythm to music they cannot hear. The film ends with a conversation between the mother of the deaf child and a young woman deaf from birth who has trained at this school.

It is an absorbing film, masterfully made with a reserved, unobtrusive technique, in which the sequences are left long enough on the screen for their natural dramatic content to be appreciated. No mention is made of the obviously high incidence of eye-defects among the young children, but clearly these cannot be treated until they have learnt to comprehend and communicate with their doctors. An admirable film, well suited for showing to a wide audience-range the advanced work carried out at the Christie Institute for the Deaf. *Brian Stanford*

912

The Development of the Rabbit

made by Gaumont British Instructional, 1943; owned by British Council; 16 mm. sound, 1280 ft. [380 m.]; 35 mm. sound, 3200 ft. [960 m.]; black and white; 40 minutes.

This film is an important contribution to the teaching of embryology, a branch of biology in which films are essential. It gives a clear and interesting account of the development of the rabbit, with references to sea-urchin, trout, frog and chick, indicating the evolutionary background of mammalian embryology.

The reproductive organs of the female rabbit are shown by dissections and supplemented with good diagrams cleverly employed. Diagrams are used to illustrate the liberation of eggs, the passage of sperm along the oviduct, and implantation of the fertilized egg in the uterus. An excerpt from the very remarkable and beautiful Canti film shows cleavage of the living mammalian egg. Early development of the egg and formation of embryonic membranes are described diagrammatically, and the progressive stages of pregnancy are shown by a series of dissections. The doe is seen eating the placentas of the newly-born young.

The "Development of the rabbit" attains a very high level as an instructional film. Photography is excellent and the judicious use of good diagrams is notable. Two improvements might be made in exposition—several unnecessary technical terms might be omitted, and the essential but unfamiliar vocabulary used in the commentary might with advantage be thrown on the screen.

The film is suitable for elementary biology students. Since it may be used for sex instruction to lay audiences, it must be

pointed out that it has limitations in this respect, its outstanding defect being the omission of discussion of the male reproductive organs. Incidentally it should be made clear that not all animals eat the placenta, lest it may be thought that humans share this habit with rabbits. *Mary Johnson*

913

The Life Cycle of Pin Mould

made by Gaumont British Instructional, 1943 ; owned by British Council ; 16 mm. sound, 370 ft. [110 m.] ; 35 mm. sound, 930 ft. [280 m.] ; black and white ; 10 minutes.

By the use of speeded-up photography, good diagrams and a commentary remarkable for its clarity and absence of technical terms, the observer can get from this film a clear and accurate picture of the life history of a common mould within a few stimulating minutes. The growth of hyphae from spores, and their ramification through the medium, the development of Sporangia and the liberation of spores are beautifully shown. Protoplasmic movements in hyphae and spores can be seen. Diagrams are used to illustrate the fusion of (+) and (−) hyphae and the formation of a resting spore. This is a most successful example of the exploitation of films for teaching biology.

Mary Johnson

[Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see page four of cover) or direct to the Editor, quoting the numbers used, e.g. Film **909**. *Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.]*

* * *

Book Reviews

AVIATION MEDICINE

914

Aviation Neuro-Psychiatry 616.8

R. N. Ironside & I. R. C. Batchelor. EDINBURGH, E. & S. LIVINGSTONE LTD., 1945. viii x 167 PAGES. 22 x 14 cm. 8s. 6d. [£0.425]

(i) The aviator and his environment ; (ii) selection for flying ; (iii) flying confidence ; (iv) the neuro-psychiatric examination ; (v) the etiology of neurotic reactions to flying, the psychological reaction types ; (vi) the psychological reaction types—their characters ; (vii) the psychological reaction types—their prognosis ; (viii) the psychological reaction types—their prophylaxis, treatment, disposal ; (ix) sickness in the air ; (x) disturbances of consciousness in the air ; (xi) neurotic visual disorders ; (xii) migraine syndrome and other types of headache ; (xiii) unclassified nervous disorders ; (xiv) head injuries—their complications and prognosis for flying ; (xv) prognosis for flying after injuries and diseases of the nervous system. Index.

The advantages of a systematic psychiatric classification based on causes are so patent and alluring that it is no wonder that unsystematic attempts at creating new causal categories are often made in psychiatry, especially when the cause in question is a prominent and widely-operating one. " Compensation neurosis " has been an instance of this in civilian life, and " shell-shock " in the 1914-18 war. Aviation, especially in wartime, affords striking evidence of the same tendency : " flying stress " and " aeroneurosis " are diagnoses that imply a direct connection between the stresses of flying and the illness to which they may give rise. Such implications have proved unacceptable on clinical grounds ; moreover, they have psychological and social consequences which may be detrimental in the same way as " shell-shock " was. But this does not mean that an all-round knowledge of clinical psychiatry gained in ordinary civilian practice will, though indispensable, in itself be sufficient to equip a doctor to deal with the special questions of aetiology, prognosis and treatment that arise in aircrew. As always with psychiatric problems, it is necessary to know the circumstances in which the patient, or the potential patient, lives and works ; and the more intimate the knowledge, the better. The application of this to aviation is very plain. Dr. Ironside and Dr. Batchelor, from first-hand experience in the field, give a straightforward account of the relationship between health and hazards in aircrew. They mention in their preface that the book has wholly been written on service overseas, far from libraries : the gain in directness, both of style and experience, much outweighs any disadvantage arising from this. The first part of this manual deals with flying and the normal individual. A preliminary chapter on physiological difficulties inherent in flying covers anoxia, the effects of acceleration (especially upon vision and consciousness), cold and fatigue. In the following chapters, on selection for flying, and on flying confidence, there is little detailed technical information, but much sense. A practical chapter on history-taking and methods of examination lead to the body of the book which deals with neuropsychiatric disorders in aviators. By means of concise case-records, the variety of clinical pictures is illustrated, and point is given to the discussion of their causation and outcome. The authors make no claim that any of the varied forms of neurotic illness they describe are peculiar to flying ; minor effects due to the special circumstances of flying duties occur, but the writers do not admit such a term as " aeroneuroses." Chapters on aetiology, symptoms, prognosis, prevention, treatment and disposal are followed by more detailed consideration of sickness in the air, disturbances of consciousness, visual disorders, headache, stuttering, somnambulism, and head injury. There is a valuable final chapter on the prognosis for flying after injuries and diseases of the nervous system.

Here and there the book reveals some of the over-simplification that is almost inescapable under wartime conditions ; for example, the reader might infer from some passages that a neurotic disorder cannot be the direct outcome of a constitutional disability. But the book is intended to be a practical clinical guide, not an exhaustive textbook : and it admirably fulfills its purpose.

CHEMOTHERAPY

915 615.778.25

The Sulphonamides In Theory And Practice

J. Stewart Lawrence. LONDON, H. K. LEWIS & CO. LTD., 1946. 125 PAGES. 21 x 14 cm. 9s. [£0.45]

(i) Introduction ; (ii) mode of action and relative potency of the sulphonamides ; (iii) pharmacology of the sulphonamides ; (iv) general considerations ; (v) organisms susceptible to the sulphonamides ; (vi) regional affections ; (vii) the sulphonamides in traumatic surgery ; (viii) toxic effects of the sulphonamides ; (ix) common abuses of the sulphonamides ; (x) sulphonamides or penicillin ; (xi) laboratory tests. References. Index.

Since the introduction of sulphonamides to clinical practice in 1935 there has been such a vast number of papers published about them that the general practitioner (together with most other people who have had reason to handle them) has been in great need of some simple guide to enable him to see the wood among all this multitude of trees. The need was met in part by the memorandum of the Medical Research Council on the Medical Uses of Sulphonamides which embodied the views of most of the British experts on this subject. But this memorandum was (intentionally) dogmatic in form and it did not give systematic references to the literature or indications of the actual results which had been reported after sulphonamide treatment of the different infections. Accordingly there was still a demand for a concise book on the sulphonamides, giving more of the background than the Medical Research Council publication did, and such a book has now been produced by Dr. Lawrence.

After a brief historical introduction, the mode of action and the relative potency of the different sulphonamides are discussed. The next chapter describes the chemical formulae and characteristics of the sulphonamides now in clinical use, together with their absorption, distribution, excretion and other pharmacological properties. Then the main principles which should be observed in the administration of sulphonamides are considered and a useful table is given, showing the dosage recommended for the different compounds in different circumstances. The following chapter describes the use of sulphonamides against infections by haemolytic streptococci, pneumococci and other organisms sensitive to these compounds. Subsequent sections deal with regional infections, e.g. those of the urino-genital tract, with dermatological conditions and with the local application of sulphonamides to wounds and burns. The possible toxic effects of these compounds are described and some abuses in their employment are noted. Finally methods are described for estimation of the concentration of these drugs in body fluids and for testing the sensitivity to them of organisms which have been isolated.

The book is well written and the author has shown skilful judgment in making his account long enough to include a summary of the main reports of each aspect of the sulphonamides but short enough to be readable and easy to consult. He recommends sulphamezathine as the most suitable sulphonamide for routine use, because of its high potency and low toxicity. But sulphadiazine is recommended for all moderate or mild infections and sulphathiazole for severe ones. Sulphapyridine has only a limited sphere of usefulness owing to its toxic effects.

The writer of any book exposes a large area to criticism, and although Dr. Lawrence has been very careful there are some points to which objection may be made. Thus, many people may think that he is unduly gloomy in believing that sulphonamides are more dangerous than a general anaesthetic and that some degree of visceral damage is nearly always produced. In the chapter on laboratory tests only a method of estimation by means of *p*-dimethyl amino benzaldehyde is described ; it would have been well if the more widely used technique of Bratton and Marshall had also been given. Sulphamezathine was surely first introduced for clinical use by workers at Manchester, even though Roblin may have recorded its examination in the laboratory at an earlier date. There are several other minor misstatements. A more important defect is due to the difficulty of preventing books of this type from becoming somewhat out of date during the interval between composition and publication. In the present instance, few important developments have occurred in sulphonamides during the past two years, but in several fields they have been replaced by penicillin to a greater extent than this book recognizes, e.g. in the treatment of staphylococcal infections ; less extensive encroachments on the field for sulphonamides will presumably be made by streptomycin. This defect is only partly remedied by the two pages discussing when to use sulphonamides and when to use penicillin which appear like a patch applied after the main part of the book had been written.

However, these are minor criticisms. The book can be strongly recommended as an account of the clinical uses of sulphonamides which is concise enough to be readable and yet gives a good account of the more important articles on each aspect of the subject. The practitioner will find it easy to consult and clear in its advice as to the action which should be taken in the different circumstances which may confront him.

F. Hawking

EMBRYOLOGY

916 611-013

A Class Book Of Practical Embryology

P. N. B. Odgers. LONDON, OXFORD UNIVERSITY PRESS, 1945. 63 PAGES ; 30 ILLUSTRATIONS. 23 x 17 cm. 7s. 6d. [£0.375]

This laboratory atlas contains a series of 27 line drawings of sections of pig-embryos (6 to 10 mm.). Each illustration is faced by a page of descriptive text. The line drawings are on a large scale and are clearly produced in black and white. The book is an admirable supplement to the student's textbook of embryology.

ORTHOPAEDICS

917

Injuries Of The Knee Joint

616.728.3

I. S. Smillie. EDINBURGH, E. & S. LIVINGSTONE LTD., 1946. xi + 320 PAGES ; 350 ILLUSTRATIONS. 25 x 17 cm. £1 15s. [£1.75]

(i) The importance of the quadriceps ; (ii) traumatic synovitis and haemarthrosis ; (iii) the surgical anatomy and physiology of the menisci and mechanism of their injuries ; (iv) surgical pathology of the menisci ; (v) clinical features of internal derangements of the knee joint relative to the menisci ; (vi) treatment, after-treatment, and complications of injuries of menisci ; (vii) injuries of ligaments ; (viii) injuries of extensor apparatus ; (ix) fractures of tibia and femur involving the knee joint ; (x) loose bodies of traumatic origin ; foreign bodies ; (xi) wounds of knee joint and surrounding tissues ; (xii) certain other injuries ; (xiii) the stiff knee. Index.

Mr. Smillie's book is a very complete and detailed account of every aspect of trauma of the knee joint. Most of the material is derived from nearly 5,000 cases of knee injury drawn from Service personnel, miners and industrial workers during the years from 1940 to 1945. The book contains much original work by the author and some new ideas which will be of interest, specially to orthopaedic surgeons even if, as the author suggests in his preface, they do not always agree with him.

The author makes a valuable contribution in the emphasis laid throughout the book on the functional result and the importance of bearing this in mind from the beginning of treatment. The importance of early and accurate diagnosis is also repeatedly stressed. It is pointed out that by these means many unsatisfactory end results can be avoided, in particular with regard to injuries of the menisci which have been the cause of a considerable loss of manpower as the result of joints being unable to stand the severe stress of modern battle-training.

The very full chapters on meniscal injuries are excellently illustrated with photographs of every type of lesion, and the extent of the author's material is illustrated by the fact that he can quote 11 cases of complete regeneration of the meniscus and 19 cases of partial regeneration. The author's own operation for repair of the anterior cruciate ligament is described. In it the medial meniscus is detached posteriorly, pared down and threaded through a hole bored in the lateral femoral condyle. For ruptured posterior crucial ligament a similar operation is described using the lateral meniscus detached anteriorly and passed through the medial femoral condyle. Too few cases have as yet been performed for any definite opinion to be formed, but results appear to be encouraging.

It has been stated that the patella has no important function, but Mr. Smillie points out that it serves to carry the extensor tendon away from the centre of rotation of the knee and so increases the mechanical efficiency of the quadriceps. For this reason a more conservative attitude to patella fractures is advocated, and he advises retention of the major fragment in cases where the injury is of moderate degree.

The book is well produced and excellently illustrated. The author is to be congratulated on the line drawings which give the impression of movement with a commendable simplicity of line. The book can be recommended as a complete and stimulating treatise on a very important subject which should be of interest and value to all surgeons.

J. W. S. L.

918 617.3(084)

Anatomical Atlas Of Orthopaedic Operations

L. S. Michaelis. LONDON, WILLIAM HEINEMANN (MEDICAL BOOKS) LTD., 1946. 67 PAGES ; 73 ILLUSTRATIONS. 25 x 19 cm. £1 5s. [£1.25]

This book is intended for quick reference and practical help to the surgeon, in particular one who does not frequently have occasion to perform orthopaedic operations. As such its place may be said to be in the surgeon's room of the operating theatre and, on occasion, in the operating theatre itself.

While not attempting to describe every operation in orthopaedic surgery, it covers a wide field of the standard approaches and procedures. Those which should be of most help to the general surgeon are the approaches to bones, joints and certain muscles

while, in addition, the book includes an outline of the more generally practised procedures, such as amputations and incisions of the hand and foot.

The description of each operation is short but clearly and concisely set out under the subheadings of position, incision, progress and notes on any particular difficulties that may be encountered. The illustrations are excellent, in particular the coloured anatomical drawings, and the book is well produced and of a practical size and shape. It should be of great value to the practising surgeon and also a very useful reference to the student for the higher surgical degrees.

J. W. S. L.

TUBERCULOSIS

919 616.24-002.5

Pulmonary Tuberculosis. A Handbook For Students And Practitioners

R. Y. Keers & B. G. Rigden. EDINBURGH, E. & S. LIVINGSTONE LTD., 1945. xii+273 PAGES; 124 PLATES. 19 x 12 cm. 17s. 6d. [£0.875]

(i) Historical survey; (ii) bacteriology; (iii) pathology; (iv) epidemiology and resistance; (v) symptomatology; (vi) examination of the patient; (vii) radiology; (viii) differential diagnosis; (ix) prognosis; (x) treatment: general principles; (xi) treatment: collapse therapy; (xii) treatment: symptomatic; (xiii) complications; (xiv) after-care; (xv) tuberculosis as a national problem. Index.

This is a new handbook addressed particularly to students and practitioners, of pulmonary tuberculosis at the present time. It includes a full description of the advances in diagnosis and treatment which have been made during the last 20 years. Sufficient information is given to give the student reader a good introduction to the subject, while the general practitioner will be enabled to obtain from it an outline of present-day therapeutic measures.

The chapters devoted to the clinical aspect of tuberculosis are the fruits of the authors' considerable experience in sanatoria. The illustrations include a number of excellent skiagrams. Some expansion of the index is called for in a book of this type.

A NEW DICTIONARY

920 61(038)=918.5

Krótki Słownik Lekarski Angielsko-Polski
Short Anglo-Polish Medical Dictionary

Opracował W. Tomaszewski. EDINBURGH, E. & S. LIVINGSTONE LTD., 1945. 168 PAGES, 14 x 11 cm. 8s. 6d. [£0.425]

This Anglo-Polish medical dictionary, the first of its kind, should be a useful addition to medical literature. During the war the Polish School of Medicine was established at the University of Edinburgh and the need for such a book became apparent. Many who attended that school acquired with their medical knowledge an acquaintance of British medical literature and a better understanding of the English language. For some time Poland will have to look abroad for much of its medical literature, and in this connection this little dictionary should prove of value. There are useful supplements dealing with weights and measures, symbols, signs and abbreviations, surgical instruments, medical schools and licensing bodies in Britain, prescribing, etc.

MEDICAL HISTORY

921 616.89(09)

The Treatment Of Mental Disorders
(Ancient And Modern)

Richard Eager. LONDON, H. K. LEWIS & CO. LTD., 1945. 100 PAGES; 7 ILLUSTRATIONS. 19 x 12 cm. 7s. 6d. [£0.375]

(i) Historic; (ii) the first mental hospital; (iii) the King is afflicted; (iv) reforms begin; (v) the building of the Devon Mental Hospital; (vi) early additions; (vii) still further extensions necessary in spite of cost; (viii) provision for the staff and further minor improvements; (ix) the medical staff; (x) the nursing staff; (xi) the chaplain; (xii) artisan staff; (xiii) general conditions of patients; (xiv) improved treatment; (xv) more modern advances; (xvi) increasing public interest.

[For review see *BMB* 884.]

922 61(092)

Battling Surgeon

Charles Brook. GLASGOW, THE STRICKLAND PRESS, 1945. 176 PAGES; PORTRAIT. 22 x 14 cm. 2s. 6d. [£0.125]

[For review see *BMB* 882.]

NEW EDITIONS

923 616.71-001.5

A Complete Outline Of Fractures
including Fractures of the Skull. For students and practitioners

J. Grant Bonnin. SECOND EDITION. LONDON, WILLIAM HEINEMANN (MEDICAL BOOKS) LTD. 1946 xiv + 658 PAGES; 693 ILLUSTRATIONS. 22 x 14 cm. £1 10s. [£1·5]

(i) General; (ii) repair of fractures; (iii) signs and symptoms of fractures; (iv) principles of treatment; (v) immediate complications of fractures; (vi) late complications of fractures; (vii) treatment of wounds; (viii) treatment of compound fractures; (ix) treatment of non-union, delayed union, and mal-union; (x) immediate operative treatment of fractures; (xi) war surgery of fractures; (xii) apparatus; (xiii) plaster of paris technique; (xiv) anaesthesia; (xv) fractures of the skull: vault and base; (xvi) fractures of the face and jaw; (xvii) fractures and fracture dislocations of the spine; (xviii) fractures of the ribs and sternum; (xix) fractures of the clavicle; (xx) fractures of the scapula; (xxi) fractures of the humerus; (xxii) fractures of the radius; (xxiii) fractures of the ulna and both bones of the forearm; (xxiv) fractures and dislocations of the carpus; (xxv) fractures of the metacarpals and phalanges; (xxvi) fractures of the pelvis, sacrum and coccyx; (xxvii) fractures of the femur; (xxviii) fractures of the patella; (xxix) fractures of the tibia and fibula individually; (xxx) fractures of both bones of the leg; (xxxi) fractures of the lower end of the tibia and fibula (ankle); (xxxii) fractures of the tarsus, metatarsus and phalanges; (xxxiii) dislocations of the jaw and upper extremity; (xxxiv) dislocations of the lower extremity. Appendices. Index.

In the five years since this book was first published much experience has been gained in the treatment of fractures, especially the compound variety, and this is embodied in the second edition which has been revised and considerably enlarged by the author, who has himself made his contribution to these advances while serving as orthopaedic specialist with the Army.

Among the additions is a chapter on the operative fixation of fractures, which covers all current methods and contains illustrations of apparatus. The inclusion here of a diagram of Parham's bands might be helpful to the modern student. A useful appendix on operative approaches to bones and joints has also been added. Another new chapter is that on the war surgery of fractures. The author lays down clearly the principle of expert treatment of the fracture as early as possible and, in the meanwhile, treatment of the wound, prevention of infection, and safe and comfortable evacuation, with a wise warning against primary suture, at any rate by the inexperienced. The Tobruk plaster and thoracobrachial box illustrate this principle and amply justify the space given them, though they are unlikely to have any prominent place in peace-time surgery and so should be mainly of historical interest to the coming generations of students.

An adequate account of the use of the sulphonamides, penicillin and proflavine has been added to the chapter on the treatment of wounds. A small omission here is that no mention is made of any adverse effect on the efficiency of penicillin in the presence of other drugs such as oxidizing agents.

The chapter on injuries of the ankle is in itself a monograph on the subject, and one feels that the author justifies the inclusion of external rotation as an additional traumatic mechanism. There is no doubt, however, that it does make the chapter complicated and perhaps difficult for the student.

As with the first edition, the book is well written and well produced with excellent illustrations. It can be confidently recommended to all students including candidates for higher surgical examinations and should also be a valuable reference for the practising surgeon.

J. W. S. L.

924 618

Recent Advances In Obstetrics And Gynaecology

Aleck W. Bourne & Leslie H. Williams. SIXTH EDITION. LONDON, J. & A. CHURCHILL, 1945. 358 PAGES; 77 ILLUSTRATIONS. 20.5 x 13 cm. 18s. [£0.9]

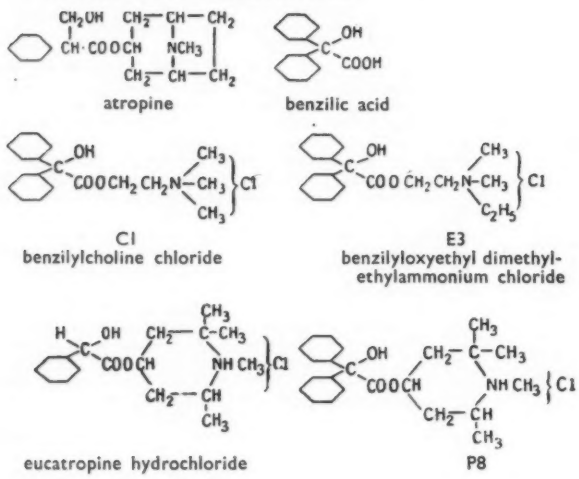
(i) Nutrition in pregnancy and foetal development ; (ii) vitamin K and haemorrhagic disease of the new-born ; (iii) anaesthesia and analgesia in obstetrics ; (iv) breech deliveries ; (v) erythroblastosis ; (vi) post-natal care ; (vii) still-birth and neo-natal death ; (viii) radiology in obstetrics, by E. R. Williams ; (ix) cancer of the uterus ; (x) sterility ; (xi) leucorrhoea ; (xii) sympathectomy ; (xiii) the sex hormones ; (xiv) ovarian tumours, by W. Shaw ; (xv) radiological investigation and diagnosis in gynaecology, by E. R. Williams ; (xvi) *x* ray therapy in gynaecology, by W. M. Levitt. Index.

Among the new additions in this latest edition of an old favourite are chapters on nutrition in pregnancy, vitamin K, stillbirth and neonatal death, and erythroblastosis. To make room for them several chapters which have appeared in two or three previous editions and in which no recent advances of importance have been made, are discarded. The remaining chapters have undergone revision. As the authors point out in their preface, isolated new facts are better in certain annual publications rather than in a book of this kind ; it is only when a body of new facts is capable of organic synthesis into a new development or of modifying an accepted line of thought on any subject, that it can claim inclusion in a book of the " recent advances " type. This sentiment is reflected in the present work, which presents an excellent digest of all the significant work which has been recorded in obstetrics and gynaecology during the past few years. Developments in some subjects are so rapid that writers of books of this type cannot hope to be completely up to date in all topics, on account of the interval between preparation and publication ; this is noticeable in a few instances in this work. Nevertheless, this book, like most others in the " Recent Advances " series, is to be welcomed.

[The prices quoted are those which obtain within the United Kingdom. Editors of overseas medical journals who wish to review publications of which notices appear are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned may be sent to the Editor if there are difficulties in obtaining them locally. Publications may be referred to by the numbers given at the left of each item, e.g. Book **914.** *It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are classified according to the Universal Decimal Classification and the classification number of each publication is given at the right.]*

Corrigendum

FIG. 1. FORMULAE OF ATROPINE AND SYNTHETIC SUBSTITUTES INVESTIGATED



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BMB **819**, Synthetic substitutes for atropine, H. R. Ing. P. 91, col. 2, Fig. 1 : We regret that the names of the compounds of which the formulae were given in this figure were accidentally omitted. The figure, including these names, should have appeared as here shown.

Addendum

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BMB **823**, p. 109, col. 2, line 33 : *After* Carden, 1944 *insert* Humphrey & McClelland, 1944

p. 110, col. 2 of References, *insert* Humphrey, J. H. & McClelland, M. (1944) *Brit. med. J.* **1,** 315

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